Department of General Medicine

Christian Medical College, Vellore

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Prevalence of hypothyroidism among women with pre-eclampsia 'THYDOR study'

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A dissertation submitted in partial fulfilment of MD (Branch I) General Medicine examination of 'The Tamil Nadu Dr. MGR Medical University' to be held in May 2018.

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CERTIFICATE

This is to certify that the dissertation titled *'**Prevalence of hypothyroidism among women with pre-eclampsia"THYDOR STUDY"**'* is the bonafide original work of Dr. Prashansa Sadanshiv, submitted in partial fulfillment of the rules and regulations for the MD (Branch I), General Medicine examination of the Tamil Dr. MGR Medical university, to be held in May 2018.

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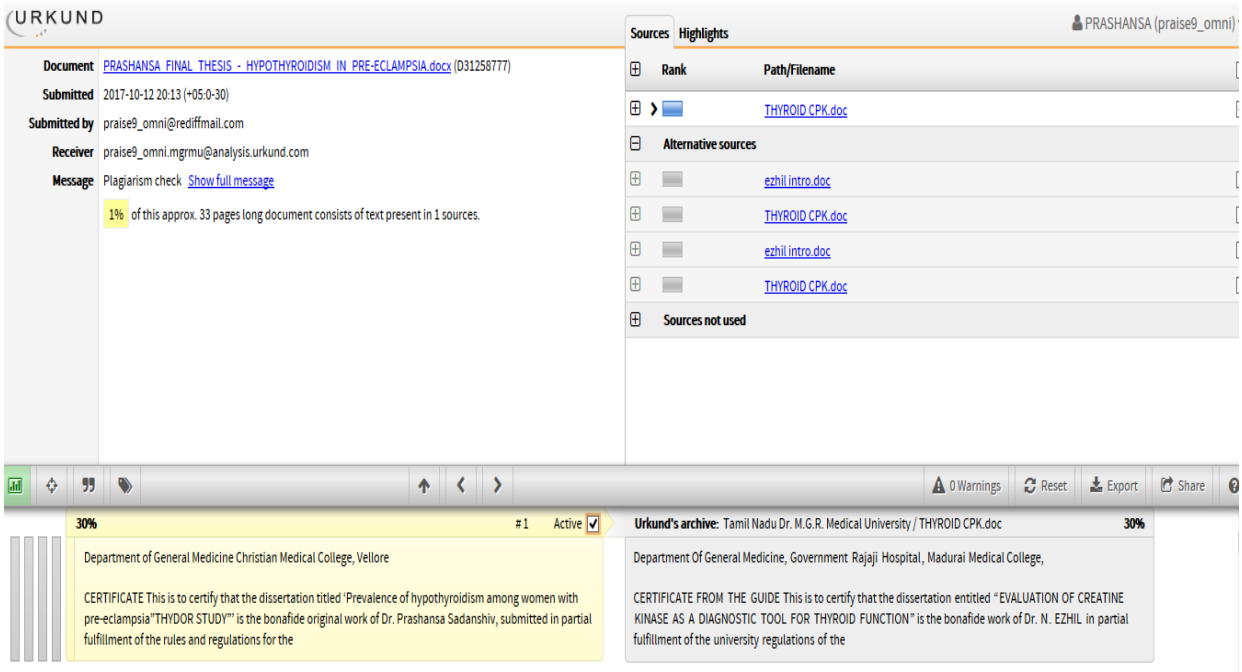

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GUIDE

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ABSTRACT

Objectives: To study the prevalence of the hypothyroidism disorder among pregnant women presenting with pre-eclampsia to the tertiary care hospital in South India. The secondary objectives were to assess the maternal and fetal outcomes, the comparison between the number of antihypertensive medications required.

Design: Single centre observational case control study

Setting: Pregnant women with pre-eclampsia in Obstetric and gynaecology ward, labour room, Christian Medical College Vellore, Tamil Nadu

Participants: 277 women fulfilled eligibility criteria, 215 were assessed, 63 in cases arm and 152 in control arm.

Intervention: Thyroid stimulating hormone for all women and if elevated thyroid stimulating hormones then thyroid function test and thyroid antibodies were assessed.

Follow up: 12 weeks

Main outcome measures: 29.3 percent women had hypothyroidism among the women presented with pre-eclampsia. Both group were similar in terms of maternal and fetal outcomes. There was no significant difference being noted in either arm in terms of secondary outcomes, though there was increased antihypertensive medication requirement noted in group with hypothyroidism. Among women with hypothyroidism 71.42 percent had subclinical hypothyroidism with 22.2 percent (10 women) being thyroid antibodies positive.

Conclusion: There is increased prevalence of the hypothyroidism disorder among the pregnant women with pre-eclampsia and is a independent risk factor. Routine assessment of the women with increased risk should be considered.

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INTRODUCTION

INTRODUCTION

Pregnancy is a state with various hormonal changes. Among these , the disorder which goes unnoticed is thyroid hypo-function.

During pregnancy, thyroid gland undergoes physiological changes. There is moderate enlargement of the gland along with increasing vascularisation. There was various factors which leads to physiological changes in thyroid gland. The few are being mentioned are there is increase in beta human chorionic gonadotropin hormone during the first trimester of the pregnancy which stimulates the thyroid gland ,due to structural analogy with the thyroid stimulating hormone. Beta human chorionic gonadotropin has thyrotrophic activity which decreased the serum thyroid stimulating hormone levels.

There is oestrogen stimulation which increases the circulating levels of thyroid binding globulin. The proposed mechanism is increased excretion of the iodine secondary to fetal intake and placenta metabolism leading to decline in the availability of iodine.

Total concentrations of thyroxine(T4) and triiodothyronine(T3) increases in first trimester of pregnancy achieving the plateau early in second trimester followed by reaching concentration 30-100% greater than the pre-pregnancy levels after the rise in thyroid binding globulin.

Thyroglobulin increases during pregnancy secondary to the enhanced activity of the thyroid gland. Hypothyroidism in pregnancy complicates pregnancy via various mechanisms. It increases the risk of pre-eclampsia. Its has been studies and found that the women with hypothyroidism during pregnancy have increased risk of preterm

labour and instrumental deliveries. They were found to have increased abortion, intrauterine death as compared to women with normal functioning thyroid.

The studies have also observed that the children born to women with hypothyroidism had lower intelligent quotient as compared to children born to women with normal functioning thyroid.

Hence this study was to assess the effects of hypothyroidism presenting with pre-eclampsia on the maternal and fetal outcomes and also whether hypothyroidism precipitates the complications of pre-eclampsia.

AIMS
& OBJECTIVES

AIM

To study the prevalence of thyroid disorder (hypofunction) in pregnant women presenting with pre-eclampsia

OBJECTIVE

Primary Objective :

To measure the prevalence of hypothyroidism in pre-eclampsia

Secondary Objective :

- To study the contribution of thyroid disorder to the maternal outcomes (mode of delivery and adverse outcomes)
- To assess the time to normalisation of blood pressures pre and post delivery
- To assess the number of medications required for the normalisation of blood pressure
- To study the fetal outcomes(IUGR/ preterm/ still birth)

REVIEW OF LITERATURE

LITERATURE REVIEW

During pregnancy thyroid disorder is found to have an increasing prevalence, especially of subclinical hypothyroidism which goes undetected in the women. There have been studies showing various adverse effects of same during the pregnancy and thereafter. Subclinical hypothyroidism is found to be one of the risk factors for gestational hypertension which had not been studied properly so far hence the etiopathogenesis have not been clear.. With thyroid disorder being a risk factor for the gestational hypertension, the incidence of the pre-eclampsia and worsening of the same was found to be high in women with thyroid disorder.

Pre-eclampsia as already known, is an important cause of maternal and prenatal mortality and morbidity in the developing countries. Pre-eclampsia can cause multi-organ involvement. It is usually characterized by new onset hypertension along with proteinuria with or without end organ damage , most often after 20 weeks of gestation in a previously normotensive patient. The exact etiopathogenesis for the same has still been on debate though there are found to be lots of contributing factors.

EPIDEMIOLOGY OF HYPOTHRYOIDISM IN PREGNANCY:

GLOBAL:

A study published in 2017, showed prevalence of hypothyroidism was found to be 17.1% in first trimester, 14% in second trimester and 5% in third trimester among pregnant women in Lebanon. The same study showed increased miscarriages to about

2.9 times along with increased pre term delivery with prevalence being 14.6%.There was also increased instrumental and caesarean section noted among the group with hypothyroidism. [i]

A study in United Kingdom showed prevalence of 2.5 percent during pregnancy with impaired intelligent quotient noted among children born to women with hypothyroidism. [ii]

NATIONAL:

In 2015 a study done in Haryana among pregnant women in their first trimester showed the prevalence of hypothyroidism being 21.5 percent had subclinical hypothyroidism.[iii]

Other study done in 2014 in North India a tertiary care centre, the prevalence of hypothyroidism was found to be 12. This study also demonstrated increased incidence of 16.6%of pre-eclampsia in women with hypothyroidism.

A study done in North India in 2013 to measure the prevalence of the hypothyroidism in pregnant women during their first trimester showed the prevalence of 14.3 percent and majority of the women had subclinical hypothyroidism. [iv]

There was adverse fetal outcomes noted in group with hypothyroidism which included spontaneous abortion 16.6%, preterm birth 33.3%, low birth weight 50% , intrauterine growth retardation 25% and fetal death 16.6% as compared to the euthyroid patients.[v]

There have been various studies which showed increased prevalence of hypothyroidism in pregnant women in North India. The studies have shown increased maternal and fetal complications secondary to hypothyroidism during pregnancy.[vi]

PATHOPHYSIOLOGY AND ITS EFFECTS :

HYPOTHYROIDISM IN PREGNANCY:

Introduction of the hormonal changes in pregnancy:

Pregnancy is a state where maternal physiology and anatomy undergo profound changes. These changes begins just after conception and evolve through the delivery following which it revert back completely. The purpose of these changes is to accommodate the need of the maternal and foetal unit.

The maternal endocrine adaptations involve changes in hypothalamus, pituitary, parathyroid, thyroid , adrenal glands and ovaries.

The hypothalamus regulates the endocrine system by coordinating input from multiple areas and output via hypothalamic pituitary axis. The axis directly affects the function of the thyroid gland, adrenal glands and gonads. This also influences growth, lactation and water balance. The hormones stimulated by hypothalamus are gonadotropin releasing hormone, corticotrophin releasing hormone, growth hormone releasing hormone, thyrotropin releasing hormone and prolactin releasing hormone. The circulating concentration of these hormones rise during the pregnancy due to placental production of identical or variant hormones.

Gonadotropin releasing hormones levels increases during the pregnancy. The main source is placenta and it plays a role in placental growth and function.

Corticotrophin releasing hormone regulates ACTH secretion during the stressful events and is expressed by placenta. Its concentration increases in maternal circulation and rises throughout the pregnancy.

Whereas growth hormone releasing hormone concentration stays same throughout the pregnancy.

The pituitary gland enlarges during the pregnancy to threefold because of hyperplasia and hypertrophy of lactotrophs which takes six month post partum period to normalise. As apposed to hypothalamic responses, gonadotropin concentration across gestation decreases which is probably secondary to high estradiol and progesterone concentration during pregnancy. Growth hormones production is reduced by 24 weeks of gestation and is replaced by rising placental derived growth hormone.

Pregnancy is a state of hypocortisolism, there is increase in serum adrenocorticotropic hormone concentration in response to corticotrophin releasing hormone produced by the trophoblast. As for the posterior pituitary hormones there is fall in antidiuretic hormone due to resetting of the osmoreceptors for antidiuretic hormone release and thirst.

The parathyroid hormone levels decline in the first half of the pregnancy , reach a nadir in the second trimester and rise thereafter.

Thyroid adaptation during the normal pregnancy:

There is increased in the metabolic needs during a normal pregnancy, hence there are changes occur in thyroid physiology. The major changes which are seen during pregnancy are [vii]

-Increase in serum thyroxine binding globulin(TBG)

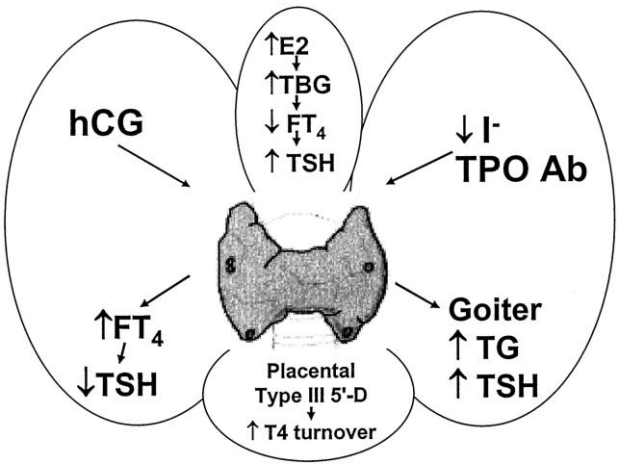
-Stimulation of the thyrotropin(thyroid stimulating hormone) receptor by human chorionic gonatropin.

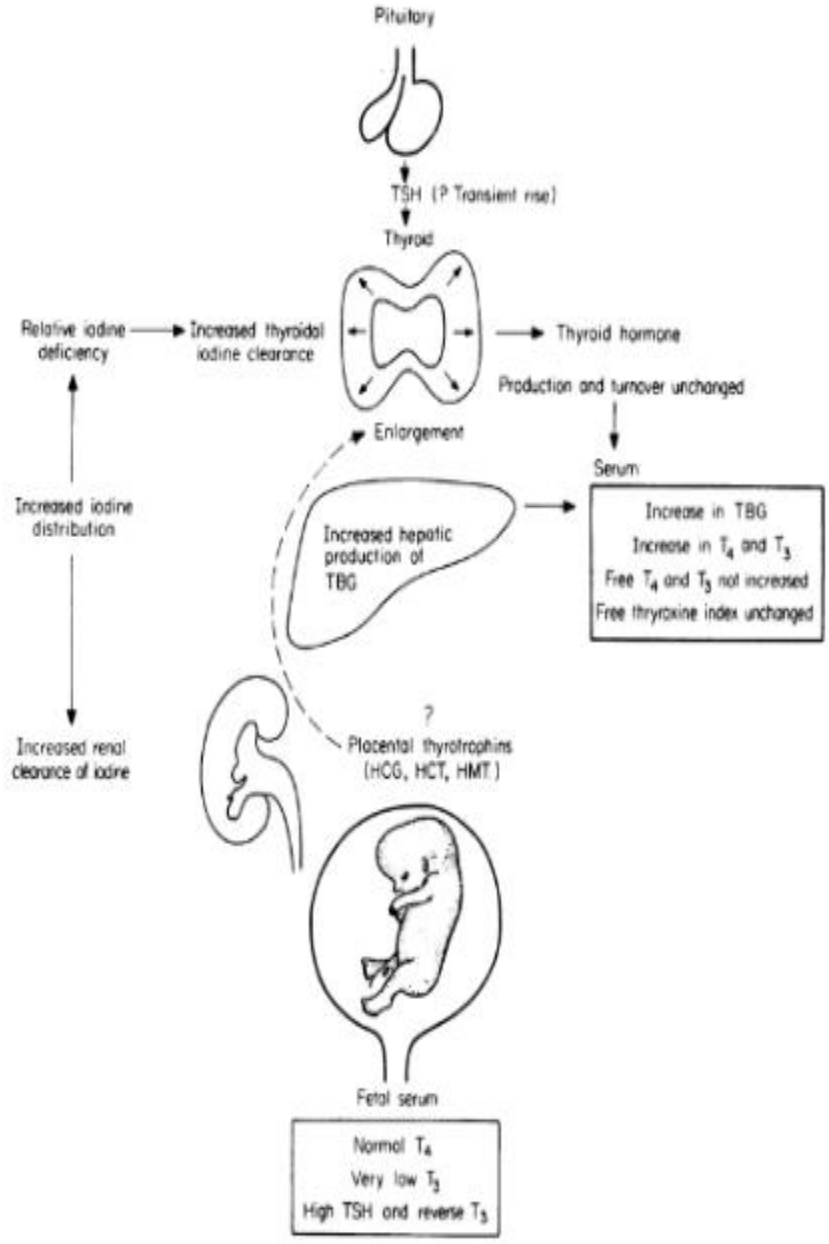
There are three thyroid hormone binding proteins- thyroxine binding globulin, albumin and transthyretin. The Albumin and transthyretin levels remain same throughout the pregnancy .The serum thyroxine binding globulin concentration increases two to three folds which is thought to be secondary to oestrogen leading to increase in thyroxine binding globulin production and sialylation, hence decreasing the clearance of the same.[viii] The other reason thought was, there is increased glomerular filtration rate of the mother which increased hepatic secretion and accelerated renal clearance of the iodide. The oestrogen cause prolongation of the half-life thyroid binding globulin from 15 minutes to 3 days.

During pregnancy there is increased need for the thyroid hormone to maintain the normal levels. To maintain the adequate free thyroid hormone level there is increased production of thyroxine and triiodothyronine by the thyroid gland. There is increase in both serum total Thyroxine and triiodothyronine levels by 30-100 percent, not the free

levels secondary to the thyroxin binding globulin. This plateau by 20 weeks and reaches a new steady state leading to pre-pregnancy rate of the overall production rate of thyroid hormones. The other cause of the increased metabolism of thyroxine in the second and third trimesters is due to a rise in the placental type II and III deiodinases, which converts thyroxine to triiodothyronine, which in turn forms a feedback mechanism for the increased thyroxine production during the pregnancy.

Beta human chorionic gonadotropin is a glycoprotein hormones which increases soon after fertilization and peak at 10-12 weeks during pregnancy. It had an weak intrinsic thyrotrophic activity. At the same time there is increase in thyroxine and triiodothyronine levels hence leading to decrease levels of thyroid stimulating hormones.[ix] This leads to transient usually subclinical hypothyroidism in all women during the pregnancy. This physiology is seen more in multiple pregnancies and hyperemesis gravidarum. At the pregnancy progresses the human chorionic gonadotropin levels normalises with normalisation of the thyroxine and triiodothyronine levels hence serum concentration rise slightly to or within the normal range.


↑E2
↑TBG
↓ FT4
↑ TSH
hCG
↓ I-
TPO Ab
↑FT4
↓TSH
Goiter
↑ TG
↑ TSH
Placental
Type III 5'-D
↑ T4 turnover


Pituitary
TSH (? Transient rise)
Thyroid
Relative iodine deficiency
Increased thyroidal iodine clearance
Thyroid hormone
Production and turnover unchanged
Enlargement
Serum
Increased iodine distribution
Increased hepatic production of TBG
Increase in TBG
Increase in T4 and T3
Free T4 and T3 not increased
Free thyroxine index unchanged
?
Increased renal clearance of iodine
Placental thyrotrophins (HCG, HCT, HMT)
Fetal serum
Normal T4
Very low T3
High TSH and reverse T3

Physiology of the fetal thyroid:

Foetal thyroid gland develops as an outpouching in the midline of the anterior pharyngeal floor. It migrates caudally to reach its final position by 7th week of gestation. The foetal thyroid has the capability of trapping iodine by 12th week of gestation and hence can synthesize thyroxine by 14th weeks of gestation. In spite of the synthesizes of the thyroxine the significant secretion is usually seen only after 20 weeks of gestation. [x] There is gradual rise in fetal TSH,T4 and TBG to adult levels by 36 weeks of gestation though T3 and free T3 do not rise to the adult levels which is secondary to placental type III deiodinase , which converts most fetal T4 to reverse T3. There is an exception which is that fetal brain have elevated levels of type II deiodinase.

Thyroid stimulating hormone transfer across the placenta is not significant. The T3 and T4 transport across the placenta can be considered significant. This is of a very special relevance in congenital hypothyroidism. There are studies which have shown umbilical cord T4 levels in neonates with congenital hypothyroidism can be up to 50% of the normal levels. [xi] The transferred T4 play a crucial role in near normal fetal cognitive development in neonates with congenital hypothyroidism. The trans placental transfer or TRH, anti thyroid drugs and thyroid stimulatory immunoglobulin have also been noted.

Transport of thyroid hormones and antibodies across placenta

Substance	Transfer across placenta
Iodine	Transferred avidly across placenta, both by passive diffusion and by active transport
Thyroxine	Some transfer is seen, especially in the first trimester
TSH	Poorly transferred
TRH	Avidly transported across placenta
Antibodies	Anti Tpo, Anti TG, TSI, TBII can all cause placenta freely and TSI can cause transient neonatal hyperthyroidism and TBII can cause transient neonatal hypothyroidism.

Definition :

Thyroid disorder is common during pregnancy due to various physiological changes. The common thyroid disorder seen is hypothyroidism which can be clinical and subclinical. A small proportion of women can present with hyperthyroidism.

Hypothyroidism in pregnancy is defined as elevated serum thyrotropin level in combination with a serum free T4 level that is within the pregnancy reference range.[xii]

Subclinical hypothyroidism is defined by elevated serum thyroid stimulating hormone concentration higher than the upper limit of the pregnancy related reference range associated with a normal serum thyroxine.[xiii]

Hyperthyroidism is defined as abnormally high levels of thyroid hormones caused by an increased synthesis and secretion of thyroid hormones from the thyroid gland.[xiv]

Euthyroidism is defined as normal thyroid physiology.

Effects of hypothyroidism :

Maternal:

There are different levels of thyroid stimulating hormones been set for each trimester of pregnancy according to the various studies done.

- First trimester :0.1 to 2.5
- Second trimester : 0.2 to 3.0
- Third trimester:0.3 to 3.0

Most of the time the subclinical hypothyroidism is asymptomatic during the pregnancy and may be detected during the screening. There are multiple studies being published over the period of time which has shown adverse effects of the thyroid disorder among the pregnant women with improvement in outcome after the initiation of the thyroid supplements.

The most common cause is considered to be autoimmune thyroiditis while other causes considered were radioiodine ablation therapy, surgery and rarely central hypothyroidism. However the iodine deficiency still remains one of the leading cause of hypothyroidism world while both for overt and subclinical hypothyroidism.

The frequency of overt and subclinical hypothyroidism have been described in various studies and have found different according to the region. Though studies have concluded the frequency of subclinical is more as compared to overt hypothyroidism.

In North America, the hypothyroidism is mainly due to autoimmune aetiology whereas in India, it's a mixed scenario. The untreated hypothyroidism is associated with several complications, the most common one being preeclampsia with increased risk of preterm labour and low birth weight and also abruption placentae. There is increased risk of spontaneous miscarriage and perinatal mortality.

During pregnancy the symptoms of hypothyroidism such as fatigability, constipation, muscle cramps and weight gain are masked, hence making it difficult to make the diagnosis of hypothyroidism. The most common adverse effects of hypothyroidism seen during pregnancy are:

- Abortion
- Anemia
- Pregnancy induced hypertension and preeclampsia
- Placental abruption /Post partum haemorrhage
- Premature birth/Low birth weight /Intra-uterine fetal death /Neonatal respiratory distress

There are various studies which have shown that the presence of hypothyroidism subclinical or overt during pregnancy have increased risk of pregnancy induced

hypertension.[xv]The cause for the pre-eclampsia in hypothyroidism is secondary to the placental dysfunction and vascular abnormalities with increased oxidative stress. The endothelial cell functions are impaired in patient hence leading to hypertension in women. The release of Nitric oxide in patient with hypothyroidism is noted to be altered hence leading to endothelial cell dysfunction and vasoconstriction. The prevalence of patient with pregnancy induced hypertension and preeclampsia have been found higher in women with hypothyroidism. [xvi] The same studies have shown that the thyroid stimulating hormone level was found to be higher in patient with preeclampsia as compared to normotensive patients. Along with the thyroid stimulating hormones the other laboratory parameter found to be abnormal were hyperuricemia and low albumin levels, worsen in patient with preeclampsia. The hyperuricemia has shown a positive correlation with thyroid stimulating hormone levels in women with preeclampsia.

Apart from pregnancy induced hypertension, hypothyroidism during pregnancy can lead to gestational induced diabetes also which is contributed to impaired metabolism and insulin resistance. [xvii] This have been observed that the pregnant women with positive thyroperoxidase antibodies positive are more prone for gestational diabetes especially during the early trimester. [xviii]

The pregnancy losses such as abortion and intrauterine deaths were found to be higher in women with hypothyroidism. The studies have shown the pregnancy losses seen in women with hypothyroidism was about 5-6 times higher as compared to euthyroid women.[xix] There have been various studies which have shown that the women with subclinical hypothyroidism during their first trimester are more prone for the miscarriage as compared to later in pregnancy. The premature delivery was found to be

higher by around 11-18 percent in women with hypothyroidism. [xx]The various studies have noticed that the mean gestation age for delivery in pregnant women with hypothyroidism was found to bae around 34 weeks which led to increased risk of low birth weight, prematurity and placental abruption. This observation was found higher in women with subclinical hypothyroidism during the pregnancy.[xxi]

The interesting findings noted in various studies is that the presence of both antithyroid antibodies in any trimester was associated with preterm premature rupture of the membrane.

There have been various studies demonstrating the adverse effects of hypothyroidism both subclinical and overt during pregnancy. The below stated tablets have mentioned few studies and the pregnancy outcomes.

The adverse effects of overt hypothyroidism on pregnancy outcomes

Authors	Year of publication	Location	Type of study	Participants	Outcomes
Abalovich et al (35)	2002	Argentina	Randomized Clinical Trial	114 women with primary hypothyroidism (16 overt hypothyroidism)	Abortion, premature delivery
Wolfberg et al (37)	2005	USA	Retrospective	19,969 women (482 with treated hypothyroid disease and 19,487 without thyroid disease)	Pre-eclampsia
Idris et al (36)	2005	England	Retrospective	167 pregnant women	Low birth weight caesarean section
Cleary Goldman et al (33)	2008	USA	Prospective	10,990 pregnant women	Preterm labor , macrosomia, gestational diabetes
Sahu et al (32)	2010	India	Prospective	633 pregnant women	Pregnancy-induced hypertension, intrauterine growth restriction, intrauterine demise, Neonatal complications, gestational diabetes
Hirsch et al (38)	2013	Israel	Retrospective case series	306 pregnant women (101 with hyperthyroidism and 205 euthyroid)	Abortions and premature delivery
Männistö et al (26)	2013	USA	Retrospective	223512 singleton pregnancies	**Primary hypothyroidism**: Preeclampsia, superimposed preeclampsia, gestational diabetes, preterm birth, induction , cesarean section, intensive-care unit admission **Iatrogenic hypothyroidism**: placental abruption , breech presentation, cesarean section after spontaneous labor

The adverse effects of subclinical hypothyroidism (with/without thyroid autoimmunity) on pregnancy outcomes

Authors	Year of publication	Location	Type of the study	Participants	Outcomes
Subclinical hypothyroidism without control of TPOAb					
Abalovich et al (35)	2002	Argentina	Prospective	114 women with primary hypothyroidism (35 subclinical hypothyroidism	Abortion, premature delivery
Stagnaro-Green et al (42)	2005	USA	Prospective (nested-case control)	953 women	Very preterm delivery
Casey et al (29)	2005	USA	Prospective	25,756 women	Placental abruption Preterm birth
Cleary-Goldman et al (33)	2008	USA	Prospective	10,990 patients	Subclinical hypothyroidism was not associated with adverse outcomes.
Sahu et al (32)	2010	India	Prospective	633 women	Cesarean section rate for fetal distress
Wilson et al (31)	2012	USA	Prospective	24,883 women	Severe preeclampsia
Subclinical hypothyroidism including negative and positive TPO Ab					
Negro et al (27)	2006	Italy	Randomized Clinical Trial	984 pregnant women	Pregnant women who are positive for TPOAb develop impaired thyroid function, increased risk of miscarriage and premature deliveries
Benhadi et al (43)	2009	Netherlands	prospective (cohort)	2497 women	Pregnant women without overt thyroid dysfunction, the risk of child loss increased with higher levels of maternal TSH
Karakosta et al (44)	2012	Greece	prospective	1170 pregnant women	Increased gestational diabetes and low birth weight neonates among those with of high TSH and spontaneous preterm among those without elevated TSH levels

Apart from the above mentioned adverse event , the percentage of instrumental delivery was also found to be higher in pregnant women with hypothyroidism with the highest prevalence of need for caesarean section secondary to either fetal or maternal deteriorating condition. [xxii]

Fetal and neonatal aspects of maternal hypothyroidism :

Hypothyroidism in mother can lead to various adverse events in the neonates , the most commonly seen were low birth weight, preterm delivery and very rarely respiratory distress. There have been various studies done to observe the effects of thyroxine in

fetal growth and noticed that it plays an important role in the normal development of the fetal brain.

The maternal hormone does enter the fetal circulation through the placenta circulation which was demonstrated by the presence of specific nuclear receptors and thyroid hormone levels at 8 weeks in the coelomic and amniotic fluids. There is fine tune maintained regarding the supply of adequate amounts of T3 required for the normal fetal brain development with the help of D2 and D3 iodothyronine deiodinases interaction during the gestation.

There have been studies which have shown prevalence of congenital hypothyroidism approximately 1 in 4000 new-borns born to the mother with hypothyroidism not treated during the pregnancy. About eighty five percentage have thyroid dysgenesis. Others aetiologies found were genetic disorder with various mutations. [xxiii]

Currently with increased awareness there are more screening programs as implemented. A Meta-analysis of seven studies showed significant decrease in IQ by 6.3 points in children with congenital hypothyroidism. The severity and duration of the fetal hypothyroidism reflect the level of the intellectual impairment.[xxiv] The new-borns born with low T4 levels are found to be more prone for intellectual impairment.

Derksen-Lubsen and Verkerk have suggested that " at least part of the brain damage in patient with congenital hypothyroidism is caused in utero and cannot be prevented by early treatment".[xxv]

The two changes in management- earlier initiation of treatment and high dose of L-thyroxine therapy can ameliorate impact of thyroid hormone deficiency on intellectual development.

With above mentioned need to remember that fetal hypothyroidism can be transient. The trans placental passage of thyrotropin receptor blocking antibodies occur in only women with thyroid autoimmunity. The effect lasting during the neonatal period is unclear of the same. The antithyroid drug can also cross the placenta and lead to fetal goitre and elevation of the thyroid stimulating hormone in the cord blood. Though there are studies for the effect of antithyroid drug during pregnancy and its effect and found there was no difference in the intellectual development in children with mother with and without therapy. The new born born prematurely also can also have low T4 and T3 in the first week of their life which normalises subsequently.

As mentioned above the maternal and fetal adverse events are found more in women with hypothyroidism. The common fetal outcome which were observed were low birth weight, premature, intrauterine death and among neonates , early death, respiratory distress syndrome and later in life intellectual abnormality.

As already mentioned intrauterine growth patterns are influenced markedly by the maternal thyroid function. There are multiple studies which have observed that the maternal hypothyroidism have direct correlation with low birth weight in the fetal affecting the male infants more than the female infants. This observation was found in women with hypothyroidism early in their pregnancy with significant sexual dimorphism being observed.[xxvi] The low birth weight in infants was observed both with

hyper and hypothyroidism. It was found that the hyperthyroidism and hypothyroidism individually increases the risk of neonatal low birth weight and appropriate management can prevent this complication.[xxvii] The other postulated theory for the same is the incomplete development of hypothalamic pituitary axis in the neonates born to mother with hypothyroidism, which can lead to congenital hypothyroidism in neonates. [xxviii]

Still birth and intrauterine death was found to be higher in mother with hypothyroidism. It was found higher in women with overt hypothyroidism as compared to subclinical hypothyroidism. The most common cause of the still birth or intrauterine death was found to be secondary to fetal hydrops secondary to hypothyroidism in fetus.[xxix]

During the early neonatal period, neonate born to mother with subclinical hypothyroidism have found to have increased risk of respiratory distress which can be contributed by the prematurity and low birth weight as compared to the neonate born to euthyroid mother.[xxx]

The infants born to mother with hypothyroidism have increased risk of congenital hypothyroidism and development and intellectual problems. There have been various studies which have demonstrated the same. According to the studies done in various part of the world, have demonstrated that the neonates with thyroid deficiency required special need for education. The studies have demonstrated that the national minimum standard for numeracy score was less in neonates with thyroid dysfunction and most of these neonates were found to have congenital hypothyroidism.[xxxi]

Maternal hypothyroidism and hyperthyroidism both are associated with lower IQ in children. The thyroid dysfunction can lead to lowering of the grey matter and cortex volume leading to impaired intellectual ability in the childhood. [xxxii] The children with born to hypothyroid mother were found to have congenital hypothyroidism and these children were noted to have mild to moderate neurodevelopment retardation. The outcome for the neurodevelopment retardation was not found to be affected by the diagnosis and treatment of the same.[xxxiii],[xxxiv].There are multiple studies with the same findings of lower neuropsychological scores in children with mother with hypothyroidism during pregnancy. One study done to compare the cognitive, fine and gross motor skills in children found to have congenital hypothyroidism and it was found that children with congenital hypothyroidism have compromised fine motor and expressive language skills as compared to the normal children.[xxxv]

Pathophysiology of preeclampsia:

Pathophysiology:

Preeclampsia is a disorder affecting various system of the maternal body, with a genetic predisposition occurring after 20 weeks of gestation. It is more common in first pregnancy and can affects maternal renal, cerebral, hepatic and clotting functions. The fetal affects are secondary to the placental insufficiency arising from abnormal placentation which is due to failure of trophoblast invasion leading to placental insufficiency.

There are different mechanism of preeclampsia being studied. Few being mentioned as below:

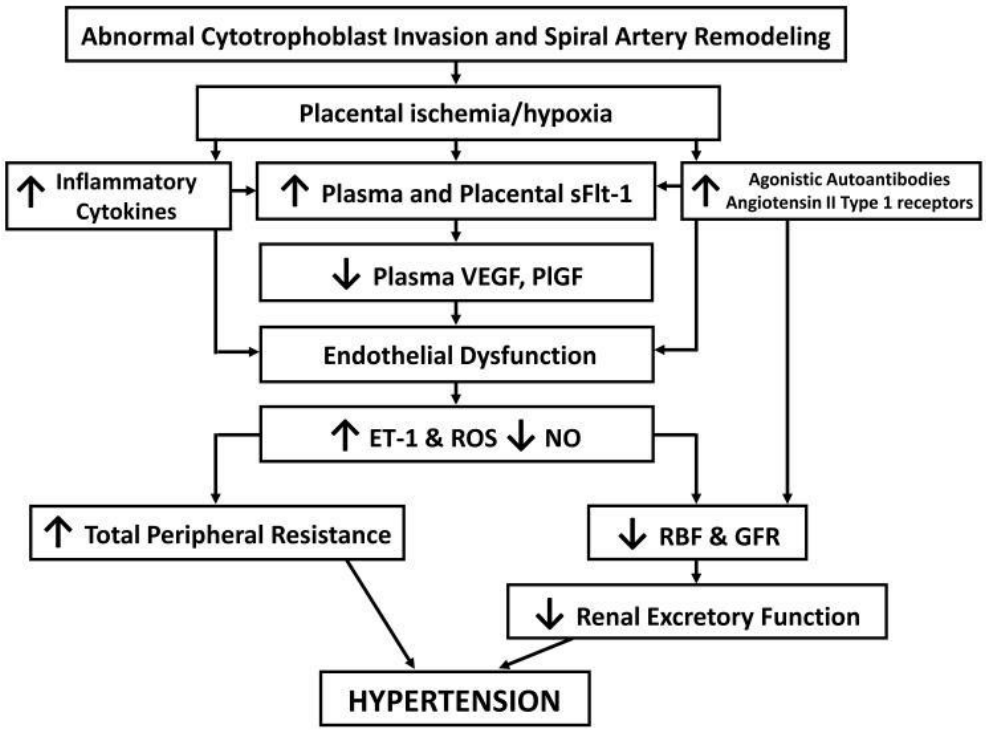
1.Abnormal placentation and vasculogenesis :

During normal pregnancy, cytotrophoblast derived from the foetus invades the maternal uterine spiral arteries, replaces the endothelium and differentiates into an endothelial like phenotype. This leads to formation of high capacitance low resistance vessels from high resistance small diameter vessels, to accommodate adequate delivery of maternal blood to the developing uteroplacental unit. In preeclampsia this process of conversion is impaired leading to persistence of high resistance vessels leading to uteroplacental insufficiency. The exact mechanism for the abnormal placental trophoblast invasion is unclear. There are number of factors being implicated in placentation including the Notch signalling pathway, the transcription factor stork head

box 1(STOX 1), various components of renin angiotensin aldosterone system and intracellular serpin proteinase inhibitor -9. [xxxvi]

Notch signalling is considered to be a crucial component of the process of fetal trophoblast cells invasion and maternal blood vessels remodelling. It is considered to play an important role in vasculogenesis by modulating differentiation and function during cell-cell contact. These trigger serial proteolytic cleavages of the receptors releasing the notch intracellular domain that translocate to the nucleus to bind to transcription factors and induces downstream targets. Absence of the notch signalling is associated with reduced spiral artery diameter and reduces the placental perfusion.

The Another described molecular pathway is STOX1 which is a member of winged helix transcription factor family. The expression of the mutation of the STOX1 related gene leads to inhibition of the trophoblast invasion leading to placental insufficiency and preeclampsia.[xxxvii]

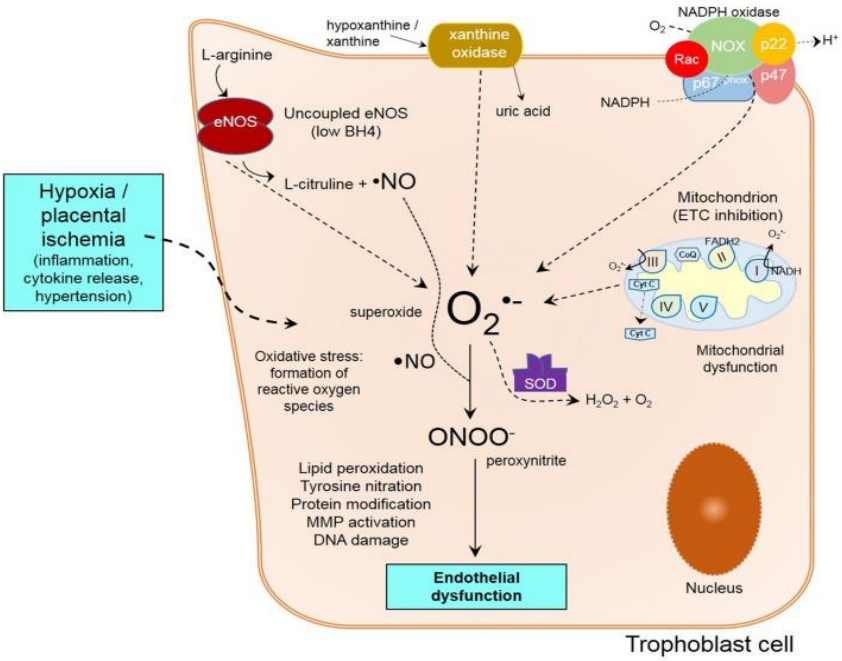


2.Activation and dysfunction of the endothelium :

The one of the important target factor in developing preeclampsia is maternal vascular endothelium. The vascular endothelium have properties such as control of smooth muscle tone through release of the vasoconstrictor and vasodilatory substances and regulation of the anti-coagulation , anti platelets and fibrinolysis functions which is by the release of different soluble factors.

As a known fact that the exchange of nutrients and waste disposal between the mother and foetus occurs via the placenta, this interface in formed during the first trimester of the pregnancy. The extra villous trophoblast from placenta invades the maternal decidua during which the maternal spiral arteries go through various conversion and form high capacitance low resistance arteries. This is impaired in preeclampsia leading to decreased blood flow to the placenta.

High refluxes of oxygen is required for the replication and proliferation along with cell maturation and embryo development. However increase in the oxygen concentration can lead to oxidative stress resulting in impairment in the above mentioned process. The placental perfusion abnormalities can lead to activation or repress the endothelial cells normal functioning. Due to the defective trophoblast invasion the arterial blood flow is impaired and results is ischemia and reperfusion state which creates a hypoxic environment favouring oxidative stress and oxidative damage with inflammation. [xxxviii]

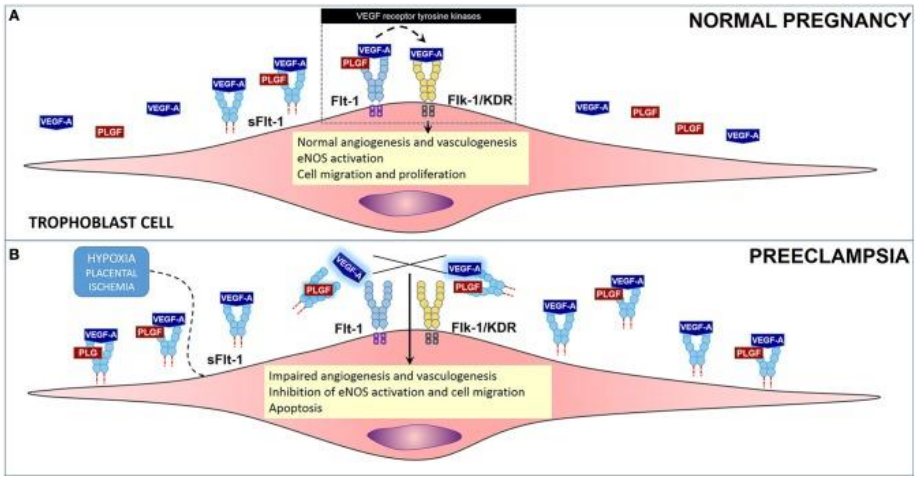


3.Factors linking placental ischemia/hypoxia with the microvascular dysfunction:

Angiogenic factors:

The circulating anti-angiogenic protein and an endogenous inhibitors of vascular endothelial growth factor are released in the circulation in response to placental hypoxia, they enter the maternal blood stream and causes endothelial dysfunction.

These factors such as vascular endothelial growth factor(VEGF) and placental growth factor(PGF) play a role in angiogenesis and endothelial cell function and health. When they are inhibited it causes impairment of angiogenesis along with impairment in the endothelial integrity maintenance. In the kidney, inactivation of free VEGF leading to endotheliosis and proteinuria.[xxxix]



Immune factors and inflammation:

Disorder of immunity and inflammation was considered to be factor predisposing pre-eclampsia and this was the first theory to be studies and proven. The theory suggest that the particles ranging from large deported multinuclear fragments to subcellular component are shed from the syncytial surface of the human placenta, these particles trigger inflammatory response. Its being speculated that the smaller particles are harmful and can be responsible for inflammatory response in maternal circulation leading to preeclampsia.

Maternal immune tolerance mechanisms is also considered to be the one of the factors in the physiology for the pre-eclampsia. This involves crucial interactions between regulatory CD4 T cells and uterine natural killer cells. If the maternal immune system fails it leads to poor implantation and poor placentation leading to the impaired placental perfusion and activation of the immune system which further leads to miscarriages.

The renin angiotensin system are suppressed in in women with preeclampsia, since they have novel agonistic autoantibody production to the angiotensin II type I receptor which can suppress the chronotropic response.

Endothelin:

This was first characterised twenty years ago as a potent vasoconstrictor. It is derived from preproendothelin which in a 203 long amino acid. It acts on smooth muscle and causes vasoconstriction and cellular proliferation. The various studies done have found that in women with preeclampsia, there is elevated levels of endothelin leading to vasoconstriction and reducing the uteroplacental perfusion. [xl]

Nitric oxide:

Nitric oxide plays an important role in modulating arterial pressure. With the help of synthetase enzymes, nitric oxide is synthesized endogenously from proteins L-arginine, oxygen and NAPDH. Its production is elevated in pregnancy and play an important role in vasodilatation. Its reduced production is controversial in preeclampsia though its deficiency is commonly seen in preeclampsia hence leading to impaired dilatation of

the vessels. The relative deficiency and its importance has yet to be explored in preeclampsia.[xli]

Oxidative and endoplasmic reticulum stress:

Oxidative stress is considered one of the factors affect the placental circulation in women with preeclampsia , During oxidative stress several oxidative markers are released such as peroxynitrite. The concentration of peroxynitrite is higher in vascular endothelium of preeclamptic women along with increased oxidative stress which precipitates placental ischemia. [xlii]

During preeclampsia there appears to be an excess of endoplasmic reticulum stress in placenta which activates number of signalling pathways altering the placental function. In women with pre-eclampsia it was noted that there is chronic endoplasmic reticulum stress process mainly in low levels especially during the second and third trimesters, which leads to the activation of growth restricted phenotype and thus increasing the levels of endoplasmic reticulum stress leading to activation of pro-inflammatory pathways which contributes to maternal endothelial cell activation. [xliii]

Hemeoxygenase:

During stress there is release of gene heme oxygenase and its catalytic product which play role in preeclampsia. There is release of heme oxygenase leads to preeclampsia and proteinuria though the effect is very modest. The heme oxygenase enzymes activities can ameliorate hypertension and hence worsen preeclampsia though there are

several evidence that supports the concept of heme-oxygenase and its product being protective against progression of preeclampsia. [xliv]

The factors predisposing to preeclampsia:

There have been various risk factors recognised by ACOG for preeclampsia such as maternal age, obesity, gestational hypertension and chronic hypertension, diabetes and multiple gestations, Chronic renal disease, previous history of eclampsia , thrombophilia, systemic lupus erythematosus, family history of eclampsia.

Gestational diabetes:

Women with gestation diabetes are found to be at higher risk of gestational hypertension and preeclampsia. The various adipokines are found to be dysregulated in gestational diabetes mellitus which impairs both metabolic and vascular function which can precipitates preeclampsia. [xlv] women with preeclampsia themselves are two to three fold increased in risk of gestational diabetes mellitus. Hence both are found to be risk factors for the other. [xlvi]

Obesity :

Obesity can lead to various metabolic abnormalities predisposing both hypertension and gestational diabetes. It have been found that overweight and obesity has higher risk of both maternal and fetal complication in the form of preterm, low birth weight and instrumental deliveries along with hypertension and diabetes in mothers.[xlvii] There are studies which have shown risk incidence of preeclampsia in mother with obesity

without diabetes with increased risk by 6 times in pregnancy complicated with diabetes.[xlviii]

The normal expected weight gain during pregnancy is 25-30 pounds for a Basal metabolic index of 18.5 -24.9 in all the three trimesters combined. For women with overweight BMI of 25-29.9 , expected weight gain is considered to be 15-25 pounds and for obese with BMI of 30 or greater weight gain expected is 11-20 pounds .

According to the American college of obstetric and gynaecology there is trimester wise required increased body weight and body mass index. Any body mass index exceeding the recommended is considered to be metabolic syndrome of pregnancy and high risk. Below is the table of the body mass index according to the each trimesters.

Prepregnancy Weight Category	Body Mass Index*	Recommended Range of Total Weight (lb)	Recommended Rates of Weight Gain† in the Second and Third Trimesters (lb) (Mean Range [lb/wk])
Underweight	Less than 18.5	28–40	1 (1–1.3)
Normal Weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25–29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	30 and greater	11–20	0.5 (0.4–0.6)

*Body mass index is calculated as weight in kilograms divided by height in meters squared or as weight in pounds multiplied by 703 divided b height in inches.

†Calculations assume a 1.1–4.4 lb weight gain in the first trimester.

Modified from Institute of Medicine (US). Weight gain during pregnancy: reexamining the guidelines. Washington, DC. National Academies Press; 2009. ©2009 National Academy of Sciences.

Preeclampsia and maternal effects::

Preeclampsia as mentioned above affects multiple organ system in the body during the pregnancy occurring after 20 weeks of gestation. Its definition and pathophysiology have been already mentioned above.

American College of Obstetric and Gynaecology have defined criteria for the diagnosis of preeclampsia:[xlix]

- Mild-moderate
  - BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and proteinuria is 300 mg/24 hours; or ≥1+ (on 2 random urine samples, collected at least 4 hours apart); or protein: creatinine ratio is ≥0.3 mg/dL.

  - BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic and in the absence of proteinuria, any of the following is present:
    - Thrombocytopenia, platelets count <100,000/uL
    - Serum creatinine ≥1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease
    - Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration.
    - Pulmonary oedema
    - Cerebral or visual disturbances.
- Severe
  - BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and proteinuria is 300 mg/24 hours; or ≥1+ (on 2

random urine samples, collected at least 4 hours apart); or protein: creatinine ratio is ≥0.3 mg/dL.

- BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and in the absence of proteinuria, any of the following is present:

- Thrombocytopenia, platelets count <100,000/uL
- Serum creatinine ≥1.1 mg/L or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function, elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary oedema
- Cerebral or visual disturbances.

According to the National Instituted for Health and care Excellence(NICE,UK) [1]criteria preeclampsia is defined as new onset hypertension (BP>_140mmHG systolic and /or >-90mmHg diastolic, based on 2 measurement taken at least 4 hours apart)occurring after 20 weeks of gestation in a pregnant women with proteinuria(urinary excretion of >-0.3gm protein in 24 hours)

It has classified preeclampsia based on severity:

- Mild: BP is 140 to 149 mmHg systolic and/ or 90 to 99 mmHg diastolic
- Moderate: BP is 150 to 159 mmHg systolic and/ or 100 to 109 mmHg diastolic
- Severe: BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic

Australia and New Zealand have different criteria. In India ACOG criteria is being followed.

Preeclampsia can present just as high blood recording with no other clinical symptoms and in severe stages can have:

Persistent severe headache

Visual problems(blurred or double vision, blind spots, flashes of light)

New shortness of breath(secondary to pulmonary oedema)

Epigastric region pain

In severe stage the blood pressure will be high (BP>160/110) with renal dysfunction , thrombocytopenia, abnormal liver test and pulmonary oedema.

Apart from above it can also cause preterm labour, abruption placentae and postpartum haemorrhage.

Preeclampsia can proceed to eclampsia causing seizure. It worse case can cause HELLP syndrome which is characterised by haemolysis, elevated liver enzymes and low platelets.[li]

The process is completely reversed by the delivery of the fetus and placenta, but the fetus are usually compromised due to the effects of the same and their survival becomes low.

Fetal:

In preeclampsia there is placental insufficiency hence decreased oxygen and nutrition supply to the fetus. Following abnormality can be seen to observe the effect of preeclampsia:

- Abnormal non stress test or biophysical profile score
- Slowed growth of the baby, usually noted by the ultrasound examination
- Decreased amount of amniotic fluid(oligohydramnios)
- Decreased blood flow through the umbilical cord by Doppler test

In foetus it can lead to intrauterine growth restriction, prematurity and preterm labour. The main impact of preeclampsia is intrauterine growth retardation which is secondary to uteroplacental insufficiency. There are multiple short and long term effects. Due to altered fetal growth it results in fetal liability. Fetal health is greatly compromised, leading to fetal morbidity and mortality.

The long term effects are seen in infants with intrauterine growth retardation, they are at higher risk of developing hypertension, coronary artery disease and diabetes in adult life.

Many foetuses have to adapt to a limited supply of blood and nutrition and hence they permanently change their structure and metabolism which later in life can lead to coronary artery disease, diabetes and hypertension. [lii]

Hypothyroidism can predispose to preeclampsia and preeclampsia can lead to both short term and long term effects in mother and fetus.

Thyroid disorder in pre-eclampsia and its effects:

Thyroid disorder both hypothyroidism and hyperthyroidism are individual risk factor for pregnancy induced hypertension and preeclampsia. There are various way through which thyroid dysfunction can precipitates hypertension though its not been studied properly. There have been various studies which have demonstrated that hypothyroidism leading to preeclampsia or worsen chronic hypertension during pregnancy.

The various theories postulated for the hypertension in women with thyroid disorder were

I. Systemic and renal vascular smooth muscle contraction leading to increased diastolic hypertension– increased peripheral vascular resistance and decreased tissue perfusion

II. Thyroid can affect the sympathetic nervous system leading to increase plasma levels of nor adrenaline (increased alpha adrenergic receptor and decreased beta adrenergic receptor– decreased cardiac beta receptor and increases peripheral vascular resistance)

III. Hypothyroidism can cause an increase in total body water with reactive decrease in intravascular volumes and hyponatremia – decrease in glomerular filtration rate (limiting the delivery to distal diluting segment)

IV. TSH- decreases anti diuretic hormone

V. It is associated with proteinuria resulting in excretion of thyroxine and thyroid binding globulins.

VI. TSH can act as a tissue specific angiogenesis in physiological and pathological conditions thus increases levels of VEGF.[liii]

As mentioned above thyroid disorder in pre-eclampsia have various mechanism and adverse events. As mentioned hypothyroidism causes contraction of the systemic and placental vascular smooth muscles leading to the increase in the peripheral resistance and diastolic hypertension which in turn decreases the tissue perfusion and placental insufficiency, this leads to worsening of the underlying pre-eclampsia or precipitates pre-eclampsia and causes placental insufficiency. [liv]

There have been studies done to show the effects of the thyroid stimulating hormones in mother and they have noticed that the higher the levels of the thyroid stimulating hormone , the worse the progression to pre-eclampsia and its adverse events.[lv] The studies have shown the women with recurrent pre-eclampsia apart from the traditional risk factors they were noticed to have thyroid dysfunction which was untreated, hence it can be expressed as thyroid disorder as a risk factor if not treated for the recurrent pre-eclampsia. [lvi]

When pre-eclampsia is complicated with hypothyroidism either overt or subclinical it was noted that there were increased maternal and foetal adverse events on the form of placental abruption, post partum haemorrhage and cardiac dysfunction. The studies have shown that the treatment of the thyroid disorder improves the outcome events both maternal and foetal. [lvii]

As mentioned the thyroid disorder can complicate pregnancy and is a risk factor for pre-eclampsia hence this study was to observe the complication and adverse event secondary to hypothyroidism in women with pre-eclampsia and to show the need for the routine screening for the thyroid disorder in women with high risk.

Materials and Methodology

Material and methodology:

Participants:

Patients 18 years or old and less than 35 years presented after 20 weeks of gestation with new onset hypertension along with proteinuria.

a.INCLUSION CRITERIA :

- All women presented with pre-eclampsia for the first time

b. EXCLUSION CRITERIA:

- Presentation before 20 weeks of gestation
- Age>35years or < 18 years
- Known case of gestational hypertension
- Known case of thyroid disorder
- Obesity(based on trimester BMI)
- Diabetes (gestational diabetes and pre-diabetes mellitus)
- Renal disease
- Previous history of eclampsia or gestational hypertension
- Twin gestation

- APLA syndrome

Background and rationale:

There have been increasing prevalence of preeclampsia and its related complications and one of the individual risk factor is hypothyroidism which remains as a asymptomatic disease during pregnancy due to overlap with pregnancy's hypermetabolic state and hence it goes undiagnosed . There have been studies to show that the maternal and fetal complications were found to be higher in women with undiagnosed hypothyroidism during the pregnancy. Therefore it is considered that screening for thyroid dysfunction and treatment of the same can prevent preeclampsia progression and complications. "THYDOR' study was to assess the prevalence of the thyroid disorder in women with pre-eclampsia and its related complications.

OBJECTIVES:

Primary objective:

To measure the prevalence of hypothyroidism in pre-eclampsia

To measure the prevalence ,all the women presented with pre-eclampsia for the first time

were assessed and if satisfying the inclusion and exclusion criteria, blood was drawn in red non heparinized container, which was processed and thyroid stimulating hormone was measured and hypothyroidism was identified based on the trimester specific normal

range. If thyroid stimulating hormone was found to be elevated above the trimester specific normal range, thyroid function test was done and for women who were found to have overt hypothyroidism , thyroid antibodies was done.

Secondary Objective :

1. To study the contribution of thyroid disorder to the maternal outcomes (mode of delivery and adverse outcomes)-

   Each women were assessed for the maternal outcomes in terms of complications secondary to the pre-eclampsia and progression to eclampsia. There was observed for the type of delivery and indications for the instrumental delivery and fetal outcomes in terms of preterm, low birth weight or intrauterine death.

2. To assess the time to normalisation of blood pressures pre and post delivery -

   To assess the time to normalisation of the blood pressure, women were followed every alternate days in the ward and after discharge outpatient based follow up was done, each visit blood pressure was monitored and assessed for the need of antihypertensive.

3. To assess the number of medications required for the normalisation of blood pressure -To assess the number of antihypertensive required , each women underwent strict blood pressure monitoring during the in hospital stay and during outpatient visit and they were

assessed for the need for antihypertensive medications and dose of drugs were optimised accordingly.

4. To study the fetal outcomes(IUGR/ preterm/ still birth) –

   At the time of delivery, new born were assessed for complication such as preterm, prematurity, low birth weight, still birth and intrauterine death and also for the medical termination of pregnancy and indications.

STUDY DESIGN:

The 'THYDOR' study is an observational case control study to measure the prevalence of hypothyroidism in women presenting with pre-eclampsia. The intervention was measuring trimester specific range thyroid stimulating hormone in the biochemistry laboratory using the standard approved technique.

After obtaining the approval from the review board, all pregnant women with pre-eclampsia presenting for the first time in the labour room and ward of the obstetric department in Christian Medical College Vellore were assessed for the eligibility criteria.

Thyroid stimulating hormone was done for all the women using Siemen's chemiluminescence immunoassay which is a standard method of measuring thyroid stimulating hormone in an individual. After assessing the thyroid status for women with

trimester specific range, women was were found to have hypothyroidism were assessed for the whether its subclinical or overt hypothyroidism by measuring thyroid function test. If thyroid function test were found to be low, women were diagnosed with overt hypothyroidism and thyroid antibodies were measured. All women were closely followed up during their in hospital stay and outpatient visit for the blood pressure and need for the antihypertensive. All women were assessed for the complications secondary to pre-eclampsia complicated by thyroid disorder and compared with women with pre-eclampsia with normal functioning thyroid. The new born born to the mother were also assessed for the complications at the time of the birth.

After obtaining the written informed consent

i. Following were assessed only at baseline:

1.Demographic details:

The demographic questionnaire contained age, gestational age, expected date of delivery and assessment date along with education level, occupation, family history of hypertension, diabetes and thyroid disorder, previous significant family history, Pre pregnancy weight and height and basal metabolic rate and current weight, current health status(systemic complications of the pre-eclampsia and organ dysfunction)

ii. Following were assessed at baseline and follow up visits:

Blood pressure were measured at each visit to assess for the need for the antihypertensive medications.

*Thyroid antibodies are either positive and negative. Elevated are considered positive and normal being negative.

Setting: Hospital based**,** in CMC obstetric department with collection of sample over 1 year with follow up 12 weeks post partum. Data collection starting from June 2016 .

Setting: Inpatient , Christian Medical College Hospital Vellore, Tamil Nadu

Locations: Labour room and obstetric ward

Units: Obstetric unit 3,4 and 5

Relevant dates: May 2016- July 2017

Periods of recruitment- All proven cases of pre-eclampsia fulfilling the inclusion and exclusion criteria will included

Follow up: 12 weeks post partum period

Data collection: Recruitment and blood investigation

Sample size:

Based on the previous studies, the prevalence of pregnancy induced hypertension and pre-eclampsia was found to be 10.9% and 4.8% in women with hypothyroidism .The standard deviation considered in group I being 35 and group II being 37. With 10% mean difference and effect size of 0.277778 and one sided alpha error of 5 with power (1-beta) of 80% with desired confidence interval of 95%, the required sample size calculated was 102 for cases and 306 for controls (1:4 control) in a case control study.

Two Means - Hypothesis testing for two means							
Standard deviation in group I	34.56	35	35	35	35	35	35
Standard deviation in group II	36.53	37	37	37	37	37	37
Mean difference	6	6	10	7.5	6.5	8	12.5
Effect size	0.1688	0.166667	0.277778	0.208333	0.180556	0.222222	0.347222
Alpha error (%)	5	5	5	5	5	5	5
Power (1- beta) %	80	80	80	80	80	80	80
1 or 2 sided	2	2	2	2	2	2	2
Required sample size per group	552	566	204	362	482	318	130
Total sample size	1104	1132	408	724	964	636	260
Samples in the ratio 1 : 2	368	377.3333	136	241.3333	321.3333	212	86.66667
Cases	736	754.6667	272	482.6667	642.6667	424	173.3333
Controls							
Samples in the ratio 1 : 4							
Cases	276	283	102	181	241	159	65
Controls	828	849	306	543	723	477	195

Data sources & Measurement:

The data was collected from the patient or patient's relative if the patient was unable to furnish the necessary information by direct interview at the time of enrolment using the CRF designed for this study by the principal investigator. Some of the required data required was acquired from the clinical workstation used at the institution (Clinical Workstation, Version; Christian Medical College; Department of Computerized Hospital Information Processing Services)

Data analysis and Statistical methods:

Data entry was done by the principal investigator in Epidata 3.1 form which was prepared based on data abstraction sheet and exported to SPSS for analysis.

Statistical analysis was done by Dr. Visalakshi Jeyaseelan, Department of Biostatistics, Christian Medical College, Vellore using IBM SPSS Statistics version edition.

Funding and approval funding source:

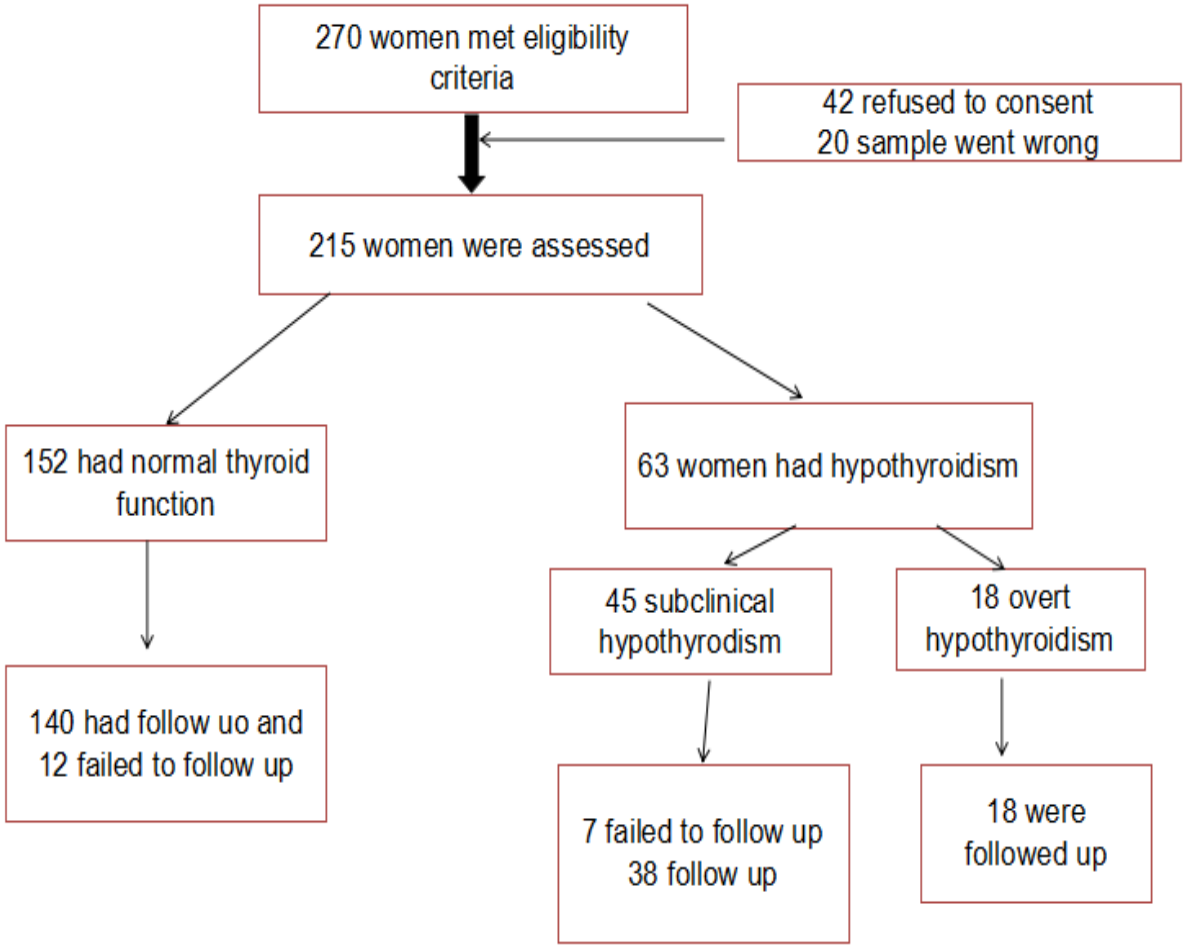
A sum of Rs.50,000 (Rupees fifty thousand only) was obtained from an institutional research grant. (Annexure 6) IRB Fund 22 Y 979 was the active account for the study. A sum of Rs 1,00,00(Rupees one lakh only) was obtained from Medicine Unit III Special fund.

Institutional Research Board approval and Ethical considerations:

The research proposal was discussed by the Institutional Review Board in 2016 and approval was obtained after receiving the suggested modifications [IRB Min No.IRB Min no.10047(OBSERVE) dated:04.04.2016]; and approved to be conducted as presented following the modifications on – April 2016.

Ethical approval was obtained prior to the study.

Strobe figure:



RESULTS

RESULTS

THESIS RESULTS:

Baseline characteristics

All the women presented with pre-eclampsia to the tertiary care centre were enrolled in the study. After obtaining the written consent , blood was drawn and thyroid stimulating hormone was assessed for each patient. Following which they were assigned in 2 group – women with hypothyroidism and euthyroid. Their demographic profile, baseline comorbidities, previous significant antenatal history and baseline laboratory parameters were assessed. The baseline characteristics in both the hypothyroid and euthyroid arm were well matched including the demographic profile, baseline laboratory parameters, basal metabolic rate, family history and previous significant antenatal history.

	Hypothyroidism	Euthyroid
Age	25.8 years	26.8 years
Gestation age	35.7 weeks	35.4 weeks
Pre-pregnancy weight	54.36 kg	56.01 kg
Height	156.05 cm	161.64 cm
Basal metabolic rate	22.17 m2	22.52 m2
Systolic blood pressure	153 mm Hg	151 mm Hg
Diastolic blood family	104 mmHg	103 mmHg
Creatinine	0.59	0.569
Platelets	218762.21	235189.14
SGOT SGPT	22.05 15.1	24.51 17.26
TSH	5.16	1.83

Results::

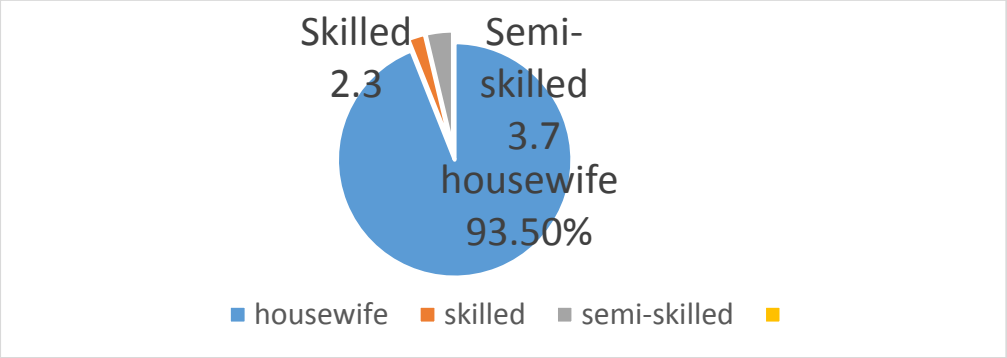
Overview of trial conduct

A total of 277 women were fulfilling the inclusion criteria from May 2016 to June 2017. Of 277 women, 42 refused to give consent for drawing the blood whereas 20 blood sample went wrong because of laboratory error. Only 215 women had their blood draw tested and followed for complication.

The mean age of the women enrolled was 26 years , and most of them presented in their third trimester with pre-eclampsia.

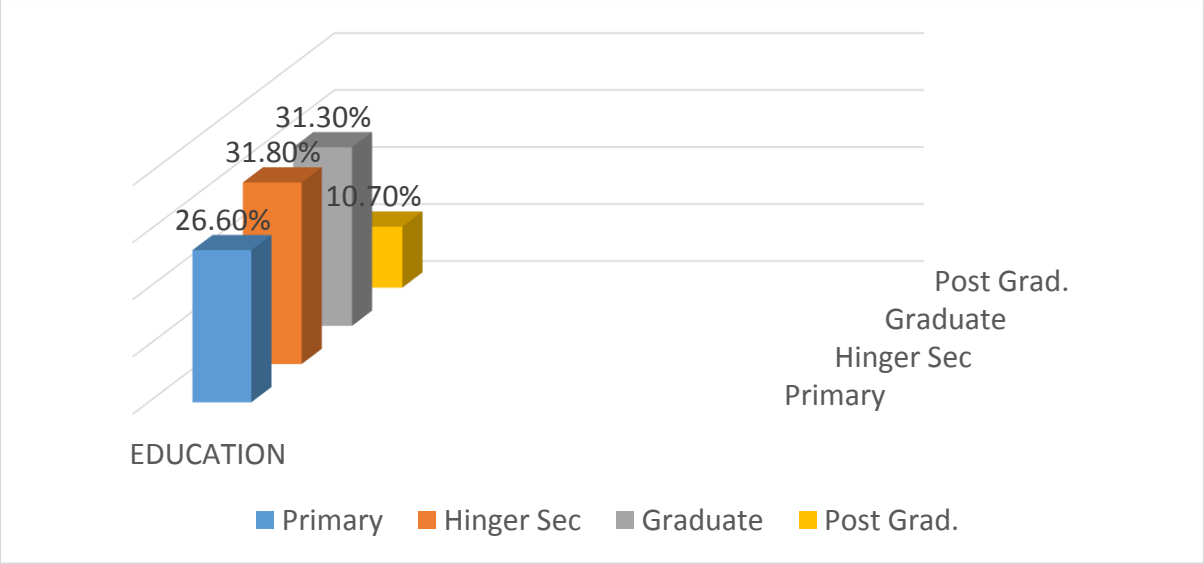
Occupation :

Most of the women enrolled were housewife with very few being working. Below is the figure to demonstrate the same:



Education:

Around 31.8 percentage of women have education up to higher secondary whereas 31.3 were graduate. Around 26.2 percent have education less then or up to primary school.



Obstetric history:

Most of the women were primigravida, around 69.3 percent whereas in 21.9 percent women this was their second pregnancy.

There were women who had previous abortion and still birth though the cause for the same was unknown. 17.7 percent had at least one abortion previously whereas around 2.3 percent of women had still birth, the cause for which was not sure.

None of the women enrolled have any risk factor contributing to the preeclampsia and its outcome.

There was no difference found in the gestational age at presentation among the hypothyroid and euthyroid women. There mean gestational age at presentation was found to be 35 weeks. The blood pressure recording at the time of admission was also found to be in similar range among women with hypothyroidism and euthyroidism. The mean systolic blood pressure was 153 and diastolic blood pressure being 106 mm of

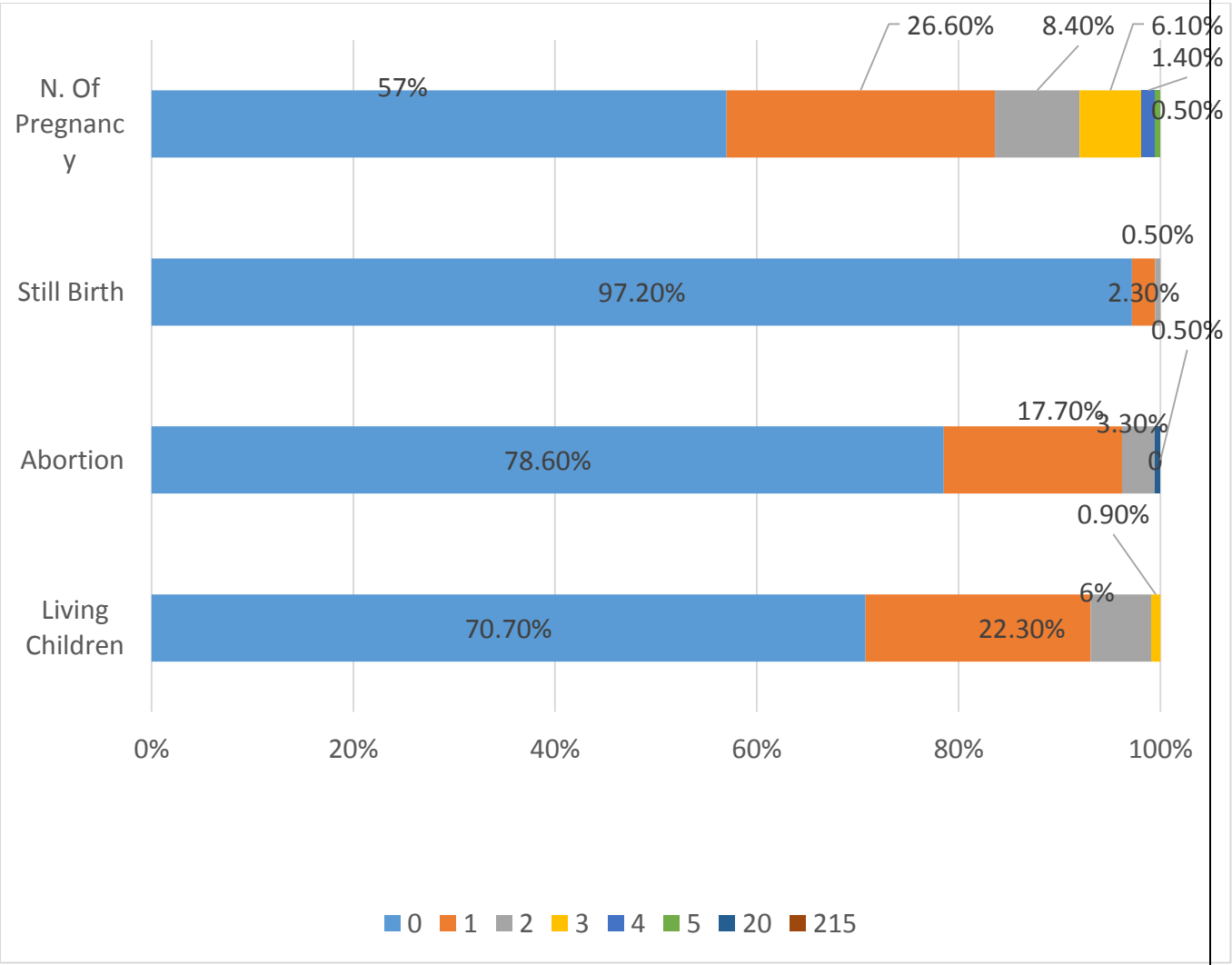
mercury. There was no difference found in the renal function and liver dysfunction in between the two groups.

There were 18 women found to have clinical hypothyroidism whereas 45 women had subclinical hypothyroidism.

Among the hypothyroidism group, 38.1 percent of women have done their graduation whereas around 31.7 percent had finished their higher secondary school and about 6.3 percent had completed their post graduation. Similar pattern was found among women with euthyroidism, 28.5 percent being graduate, 31.8 percent being post higher secondary school and 12.6 percent having being finished their post graduation.

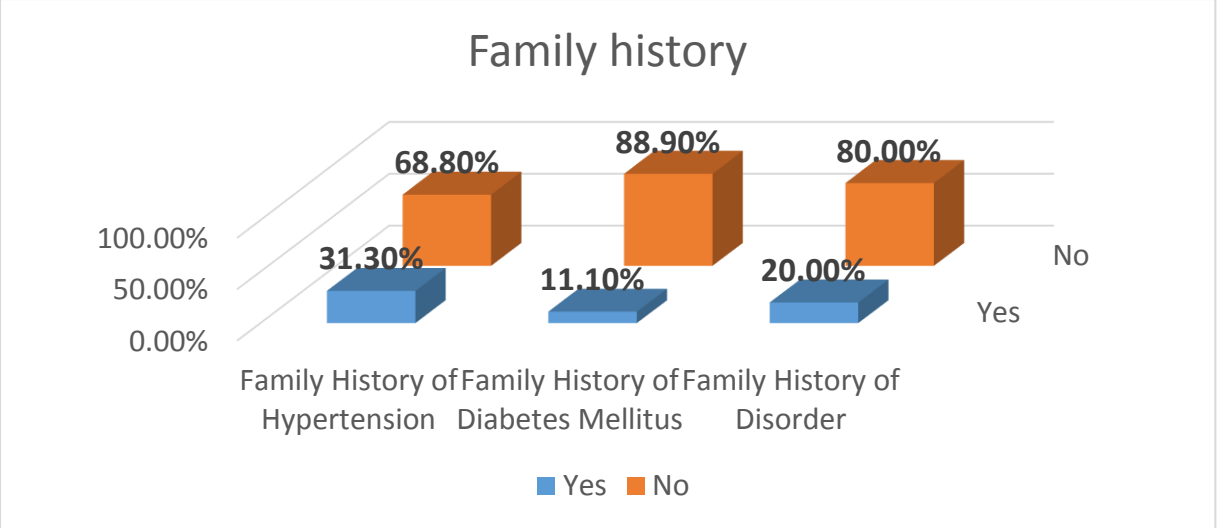
Irrespective of the education most of the women were housewives or had left their jobs comprising around 90.3 percent and 95.4 percent subsequently in hypothyroidism and euthyroidism group. Whereas only 4.8 percent and 1.3 percent were working as skilled professionals among the hypothyroidism and euthyroid group and 4.8 percent and 3.3 percent as semiskilled profession among each group respectively.

Most of the women presented with preeclampsia were primigravida comprising 77.8 percent and 65.8 percent respectively. Among women with hypothyroidism, 14.3 percent of women had previous at least one abortion whereas around 19.1 percent had one abortion in the euthyroid group. Women with hypothyroidism were noticed to have no still births in previous pregnancy whereas around 3.3 percent in euthyroid group were noted to have one still birth.

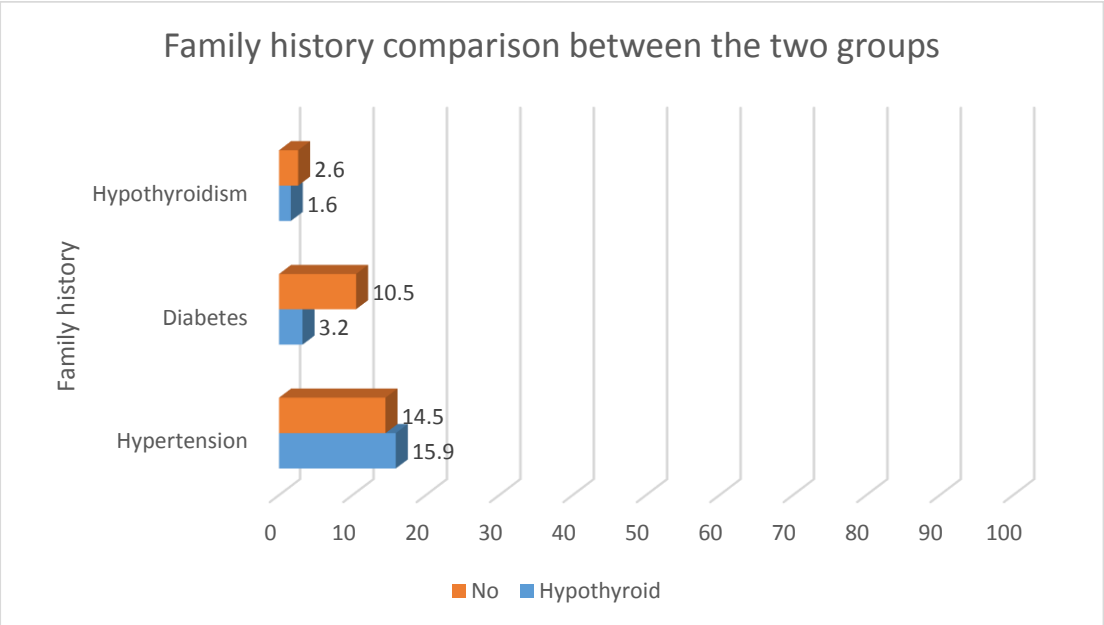


Family history:

Only 14.9 percent had family history of hypertension either in the father or mother and 8.4 percent had diabetes among family members. There was 2.3 percent of women with a family history of hypothyroidism.



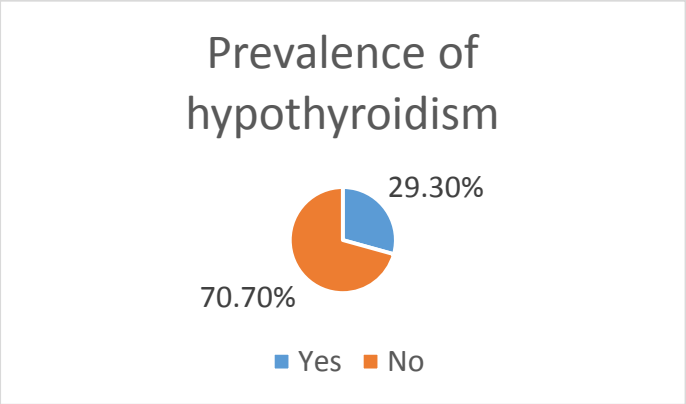
Looking at the family risk factors, among the women with hypothyroidism around 15.9 percent and women with euthyroidism around 14.5 percent had family history of hypertension in either of the parents, whereas only 3.2 percent in hypothyroid and around 10.5 percent in euthyroid group had family history of diabetes mellitus. Only 1.6 percent in hypothyroid and 2.6 percent in euthyroid group had family history of hypothyroidism including parents and siblings



Yes: women with hypothyroidism, No: women with normal thyroid function

Outcomes:

The primary outcome was to study the prevalence of hypothyroidism in women with pre-eclampsia in a tertiary care centre in South India. After testing the blood drawn , 29.3 percent women presented with pre-eclampsia had hypothyroidism either subclinical or overt hypothyroidism.



Yes: Hypothyroidism No: Normal thyroid function

Among the women who were found to have hypothyroidism, there were 18 women with overt hypothyroidism and 45 women with subclinical hypothyroidism.

The secondary outcomes were to assess the difference in the antihypertensive requirement and time to normalisation of the blood pressure and maternal and fetal complications.

Clinical symptoms:

Around 1.9 percent had features of complications in the form of papilledema. 28.8 percent women were noticed to have pedal oedema which can be secondary to

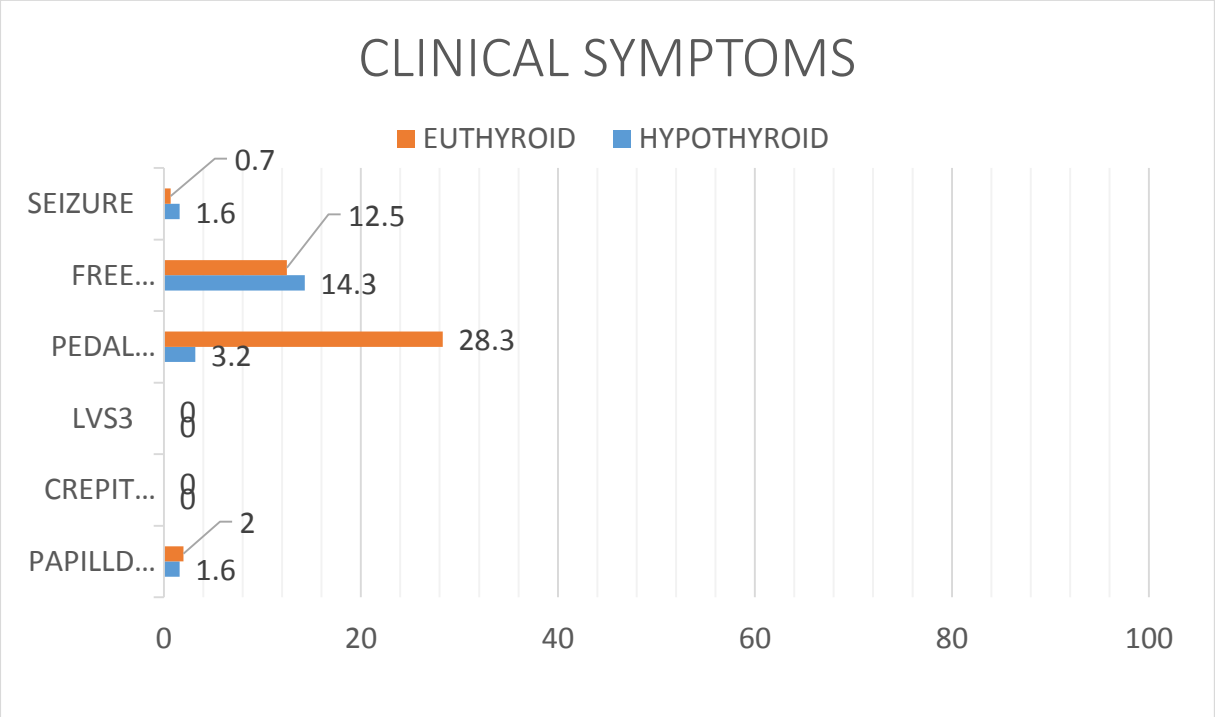
hypoalbuminemia, proteinuria in preeclampsia or pregnancy induced and 13 percent had signs of free fluid. Only 2 patients, 1 in each group (0.9 percent) progressed to have eclampsia and had seizures.

Papilledema was noticed in only 1 woman (1.6 percent) among women with hypothyroidism and 3 women (2 percent) among women with euthyroidism.

None of the women had signs of cardiac dysfunction or respiratory distress.

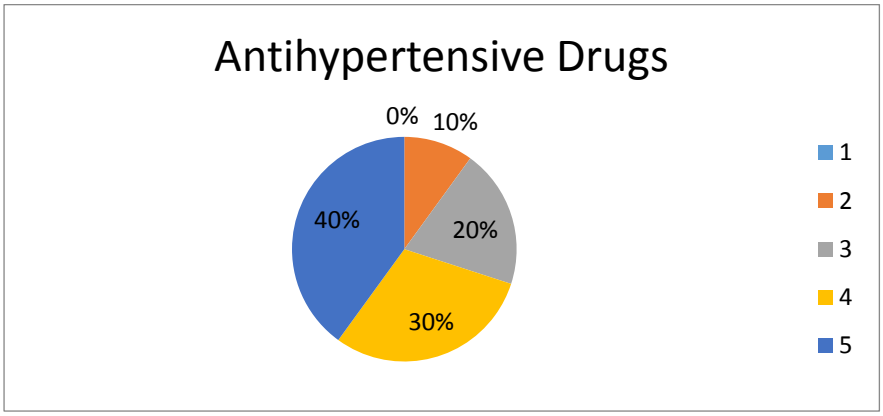
Women were noticed to have fluid overload status in the form of pedal oedema , 30.2 percent in hypothyroid and 28.3 percent in euthyroid group. Ascites was noticed in 14.3 percent and 12.5 percent of women in hypothyroid and euthyroid group respectively.

Among the women with hypothyroidism one woman progressed to eclampsia and had seizure and similar number was noticed in women with euthyroid thyroid function



Antihypertensive drugs:

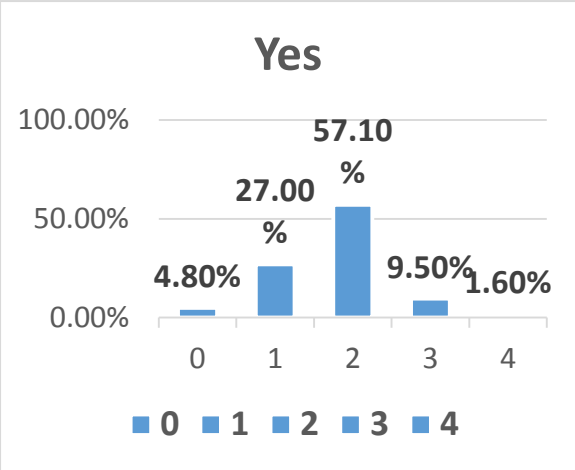
In total around 42.8 percent women required at least 2 drugs for blood pressure control and 36.7 required one drug for the same. There were 6 percent women who did not require any antihypertensive and with rest, their subsequent blood pressure were within normal limits. There were 14 percent of women who needed 3 drugs for control of blood pressure and 0.5 percent one patient required 4 drugs for the same.

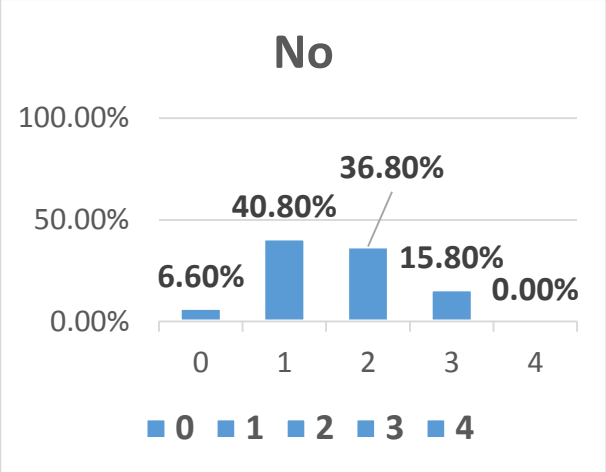


Women with hypothyroidism with regards to the antihypertensive requirement, only 4.8 percent did not require antihypertensive as compared to 6.6 percent in euthyroid group.

Among the women with hypothyroidism, 27 percent required at least 1 antihypertensive, 57.1 percent required 2 antihypertensive, 9.5 percent required 3 and only 1.6 percent required more than 3 antihypertensive for blood pressure control.

In euthyroid group, 40.8 percent required only one antihypertensive, 36.8 required 2, 15.8 required 3 antihypertensive and no women required more than 3 antihypertensive for blood pressure control.





Yes: women with hypothyroidism

No: Women with euthyroidism

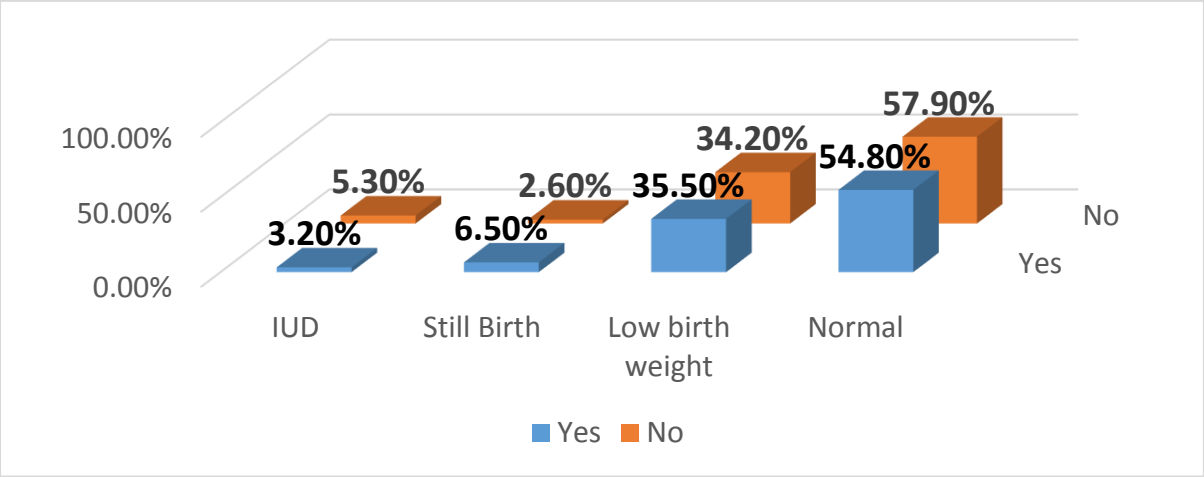
Fetal outcomes:

Most of the babies born had normal weight of the gestation at delivery time though around 34.6 percent had low birth weight and 3.7 percent were still births with 4.7 percent being intrauterine deaths.

While comparing the two groups to look at the effects of hypothyroidism, among the women with hypothyroidism, 54.8 percent of babies born had normal birth weight, 29.7 percent had low birth weight at the time of delivery. 6.5 percent were still born and 3.2 percent were intrauterine deaths.

Among the women with normal thyroid level, 57.9 percent had normal birth weight of the babies, 34.2 percent had low birth weight. 5.3 percent were still born and 5.3 percent had intrauterine deaths.

There was no difference found between the two group with regards to the fetal outcome



Mode of delivery:

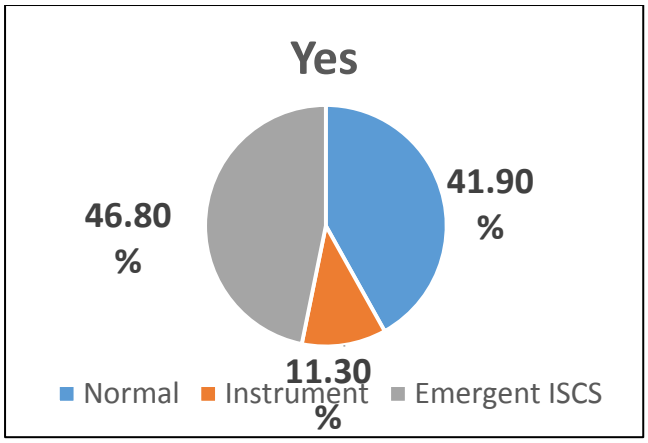
Most of the women were delivered in CMC though 1.4 percent were delivered outside, these women took discharge and were delivered in an outside hospital.

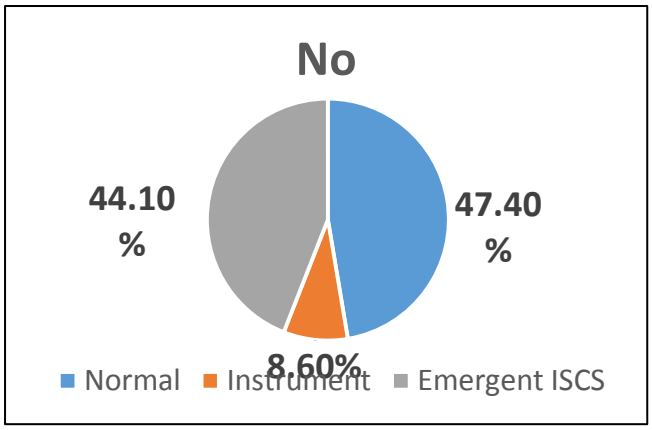
Emergency caesarean section was done in around 44.9 percent of women either due to worsening maternal or fetal condition. Though 45.8 percent had normal vaginal delivery and 9.3 percent had instrumental delivery.

The most common indication for the assisted delivery was non reassuring fetal status found in among 74.1 percent with 10.3 percent being secondary to deteriorating maternal condition and 6 percent of women had abruption placenta.

In hypothyroid group- 46.8 percent women had undergone emergency caesarean section whereas 11.3 percent had instrumental delivery, the rest had normal delivery.

In euthyroid group- 44.1 percent women had undergone emergency caesarean section, 8.6 percent had instrumental deliveries rest had normal deliveries.



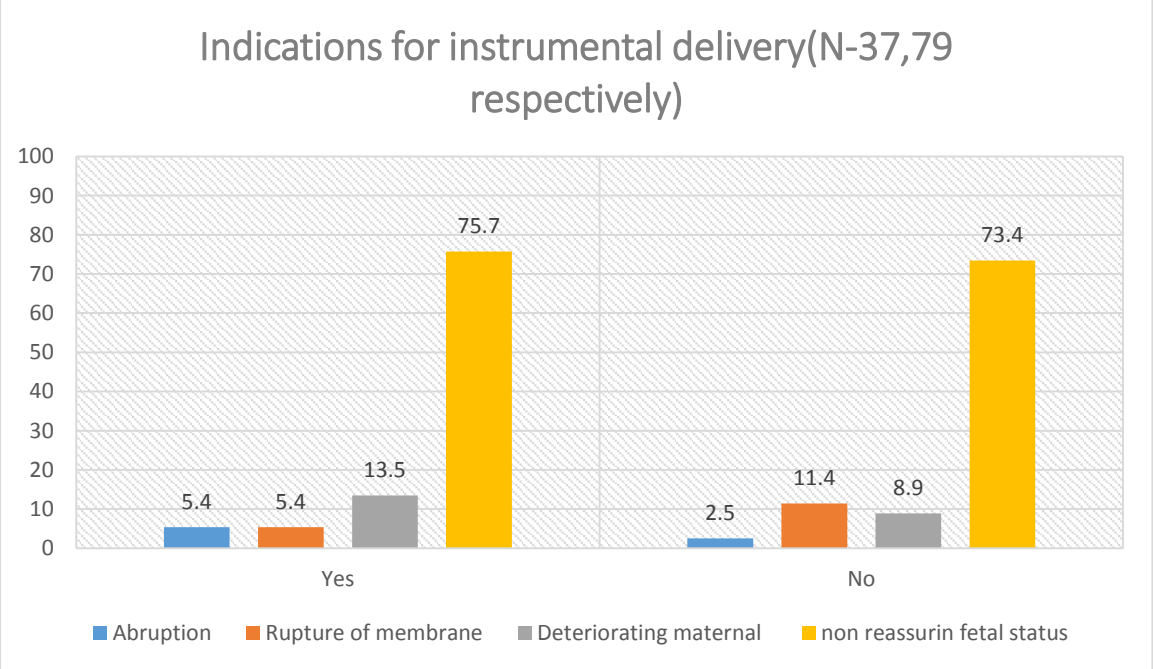


Yes: Women with hypothyroidism

No: Women with normal thyroid level

Indication for instrumental delivery:

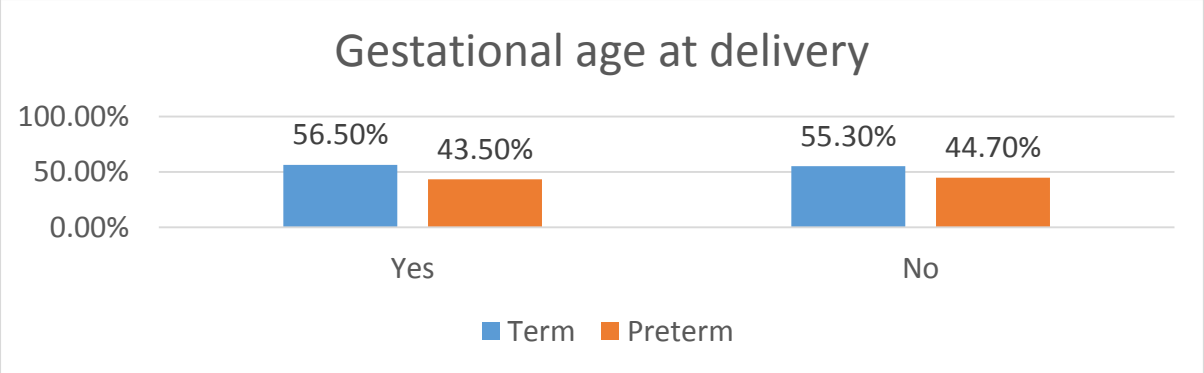
In both the group the predominant indication for instrumental or emergency caesarean section was non reassuring fetal status, 75.7 and 73.4 percent in each group respectively. Deteriorating maternal condition was noted in 13.5 and 8.9 percent in each group where as 5.4 percent and 6.3 percent of women had abruption placenta in each group.



Yes: Women with hypothyroidism, No: Women with normal thyroid function

Gestational age at delivery:

There was no difference found with respect to the gestational age at delivery in either of the group, with preterm delivery seen in around 43.5 and 44.7 percent respectively.

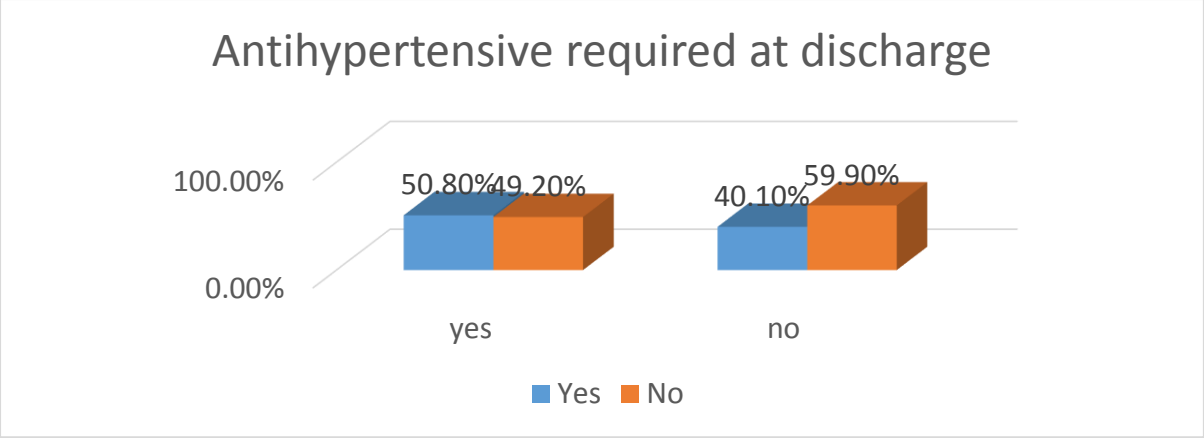


Antihypertensives at discharge:

Around 43.3 percent of women required antihypertensives at the time of discharge and 56.7 percent had well controlled blood pressuring not requiring antihypertensive at discharge.

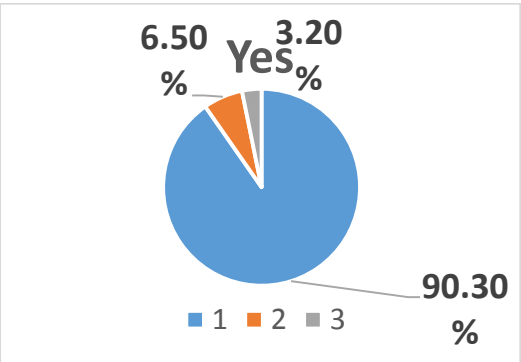
Among the women requiring antihypertensives, around 90.4 percent required only one antihypertensive with 8.4 percent only requiring 2 and 1.2 percent requiring 3 antihypertensive at discharge for optimum blood pressure control.

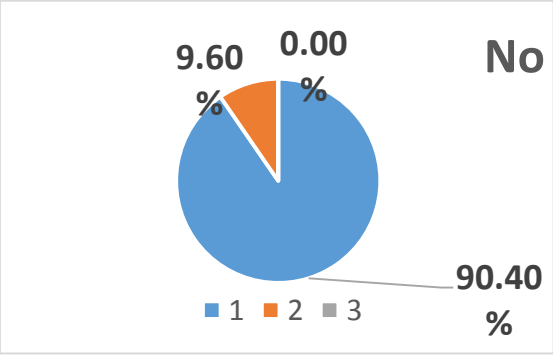
Comparison between the two groups: around 50.8 percent of women required antihypertensive at the time of discharge among women with hypothyroidism as compared to 40.1 percent in euthyroid group.



Among the women requiring antihypertensive at discharge, 90.8 percent of women in hypothyroid group required at least one antihypertensive at the time of discharge and 90.4 percent in euthyroid group. 6.5 percent required at least 2 and 3.2 percent required more than 2 antihypertensive among the women with hypothyroidism as opposed to 9.6 percent requiring 2 and none requiring more than 2 antihypertensive at discharge in women with normal thyroid function.

The below graph showed the difference between number of antihypertensive among the women requiring antihypertensive at discharge





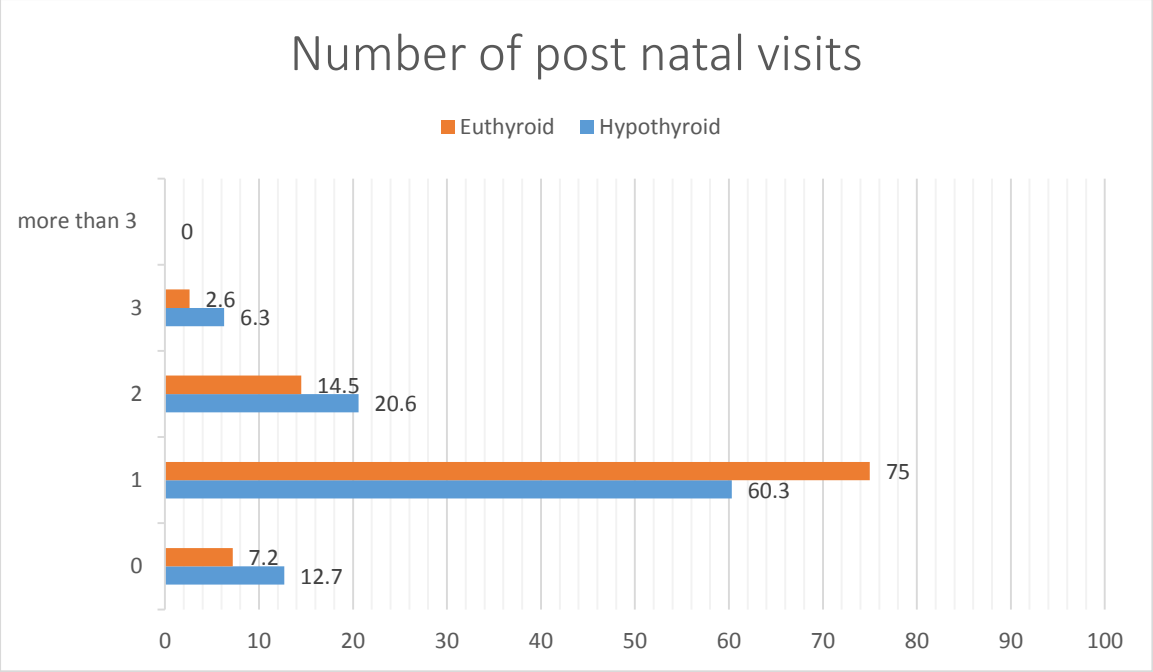
Yes: women with hypothyroidism, No : women with normal thyroid function

Post natal visits:

Around 70.7 percent women had at least one postnatal visit to hospital for the blood pressure check up with around 16.3 percent had visited at least twice and only 3.7 percent visited the hospital thrice for subsequent blood pressure monitoring. There were about 8.8 percent women who did not come for postnatal follow up for blood pressure monitoring after discharge.

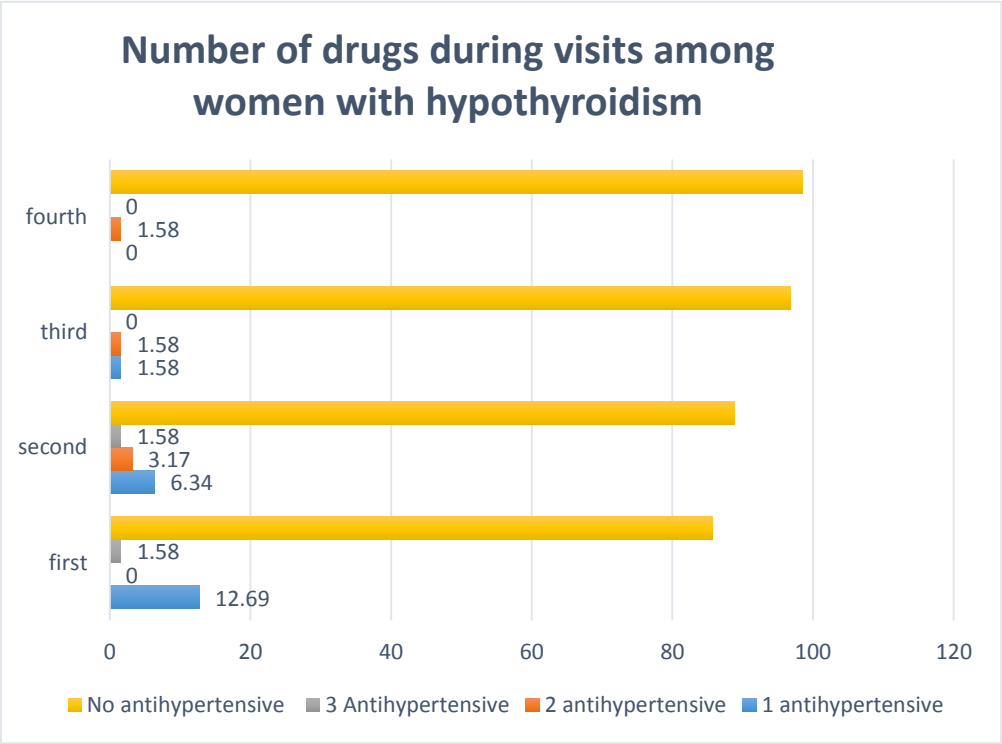
There were women who did not come for postnatal visit for the blood pressure monitoring which was about 12.7 percent and 7.2 percent in each group hypothyroid and euthyroid.

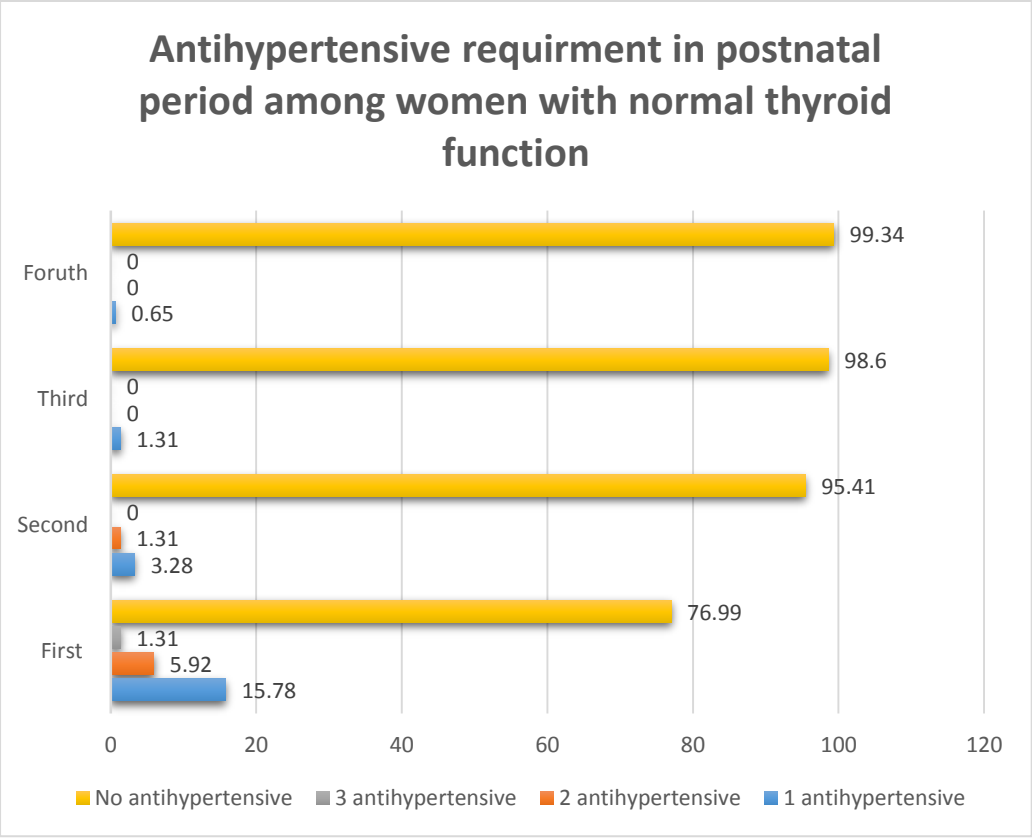
In hypothyroid group 60.3 percent women came for at least one follow up, 20.6 percent came for at least 2 follow up visits and 6.3 percent came for at least 3 follow up visits to outpatient department. In euthyroid group 75 percent came for at least one follow up, 14.5 percent came for 2 follow up visits and 2.6 percent came for 3 follow up visits to outpatient department.



Antihypertensive requirement in post natal period:

Among the 63 women with hypothyroidism, around 9 women required anti hypertensives at 2 weeks, 7 required even at 45 days follow up and 3 required at 60 days follow up. Of the women requiring antihypertensive, there was only one woman with overt hypothyroidism, rest were subclinical hypothyroidism. Only one woman required antihypertensives even after 3 months post delivery and she was found to have overt hypothyroidism. Among the women with normal thyroid function, at 2 weeks 35 women required continuation of the antihypertensives, 7 required a follow up at 45 days and 2 at follow up visits at 60 days and one required more than 3 months of antihypertensive for blood pressure control.


Number of drugs during visits among women with hypothyroidism
fourth
third
second
first
0
1.58
0
0
1.58
1.58
1.58
3.17
6.34
1.58
0
12.69
0
20
40
60
80
100
120
No antihypertensive
3 Antihypertensive
2 antihypertensive
1 antihypertensive


Antihypertensive requirment in postnatal period among women with normal thyroid function
Foruth
Third
Second
First
99.34
0
0
0.65
98.6
0
0
1.31
95.41
0
1.31
3.28
76.99
1.31
5.92
15.78
0
20
40
60
80
100
120
No antihypertensive
3 antihypertensive
2 antihypertensive
1 antihypertensive

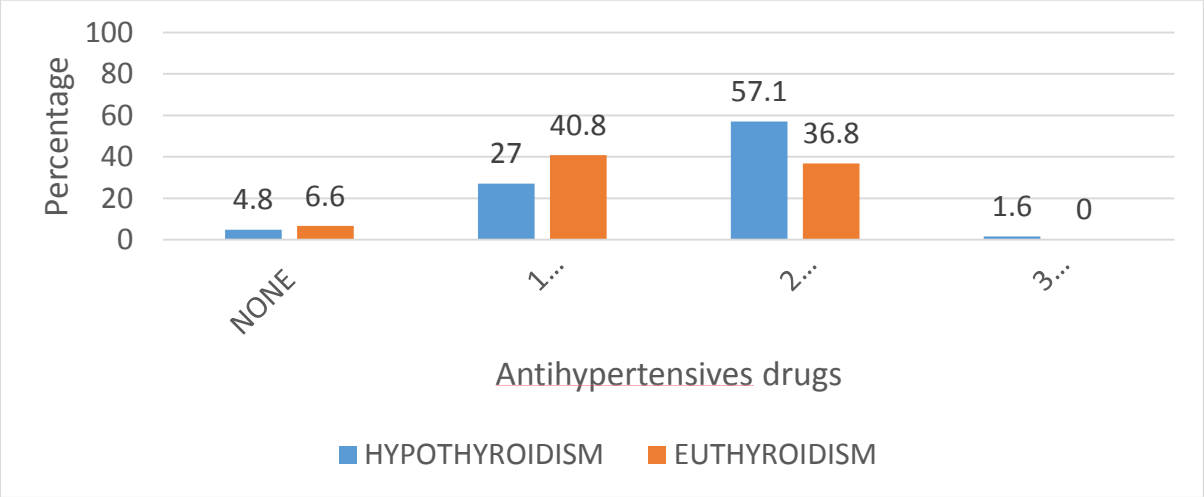
Antihypertensive requirement among the two groups:

With regards to the maternal and fetal outcomes there was no significant difference found between the two groups however there was noted difference between the groups with regards to the number of antihypertensive requirement for blood pressure control.

1. During perinatal period:

At admission prior to delivery , it was noted that women with hypothyroidism required more number of anti hypertensives for blood pressure control.

Among the women with hypothyroidism, there were 57.1 percent who required at least two anti hypertensives for blood pressure control as compared to 36.8 percent in women with euthyroidism.



2. Antihypertensive in immediate post natal period:

When compared the need of antihypertensive medications at the time of discharge, there was no statically difference found between the two groups.

3. Antihypertensive during postnatal period:

Among the women who required anti hypertensives during the postnatal period during the follow up visits, there was no significant difference found among the two groups though it was noticed that 3.2 percent only among women with hypothyroidism required 3 drugs.

Subgroup analysis:

There were 45 women who were found to have subclinical hypothyroidism and 18 women found to have overt hypothyroidism.

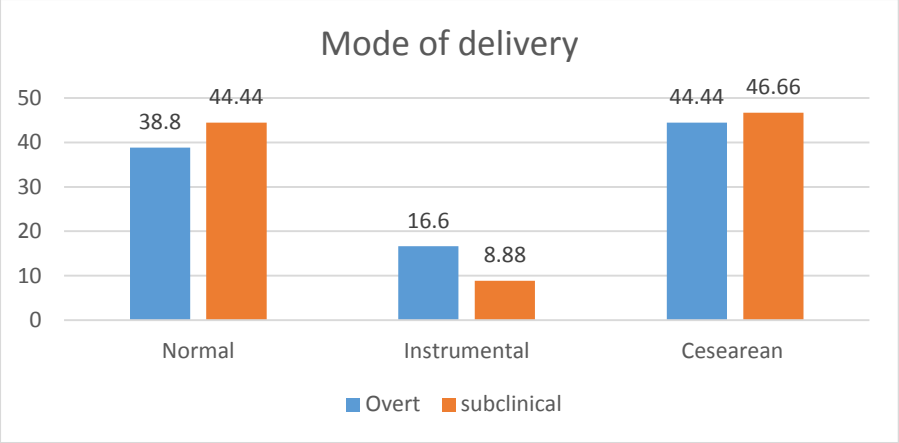
Among the women with subclinical hypothyroidism , there were 10 women with thyroid antibodies being positive.

1. **Comparison between subclinical and overt hypothyroidism:**

In terms of maternal outcomes, when compared the symptoms and gestational age at presentation, there was no significant difference found.

Maternal outcomes:

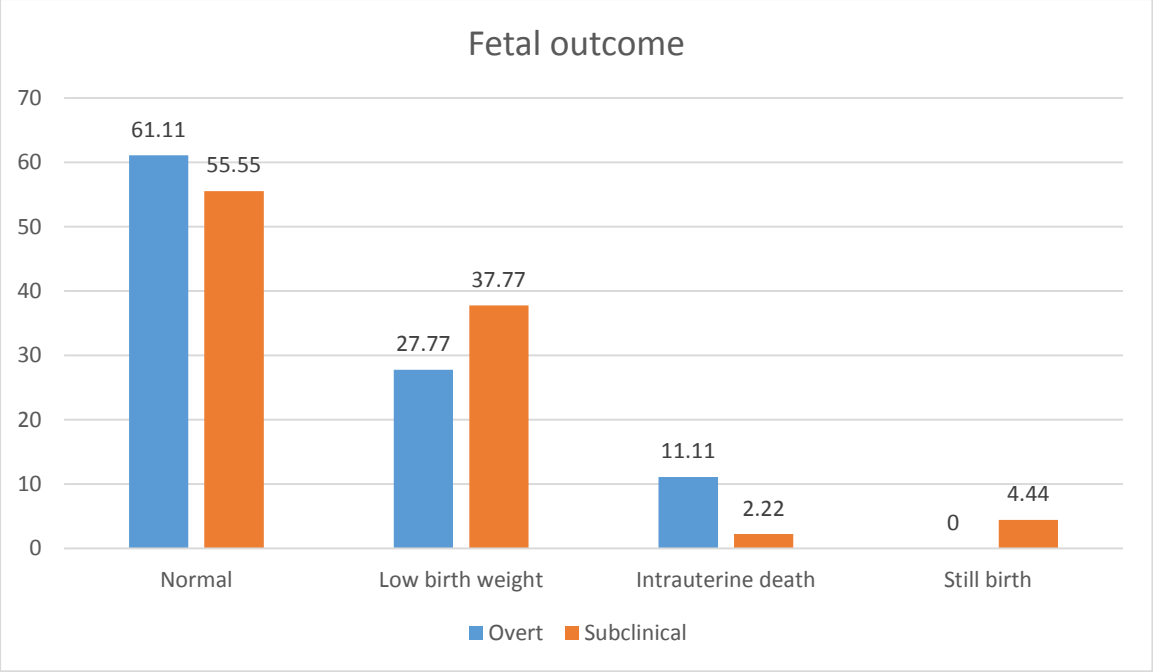
In terms of mode of delivery, there was no significant difference being noted among the two groups. Though instrumental delivery was found to be more among women with overt hypothyroidism.



When compared the indications for the instrumental deliveries, both group the main indication was non reassuring fetal status followed by deteriorating maternal condition and it was not statically significant.

Fetal outcomes :

With regards to the fetal outcomes, it was noted that still birth was slightly higher in number among women with subclinical hypothyroidism. The other significant finding noticed was that the intrauterine death was higher in women with overt hypothyroidism. There was no significant difference found among the two groups with regards to the gestational age at delivery.

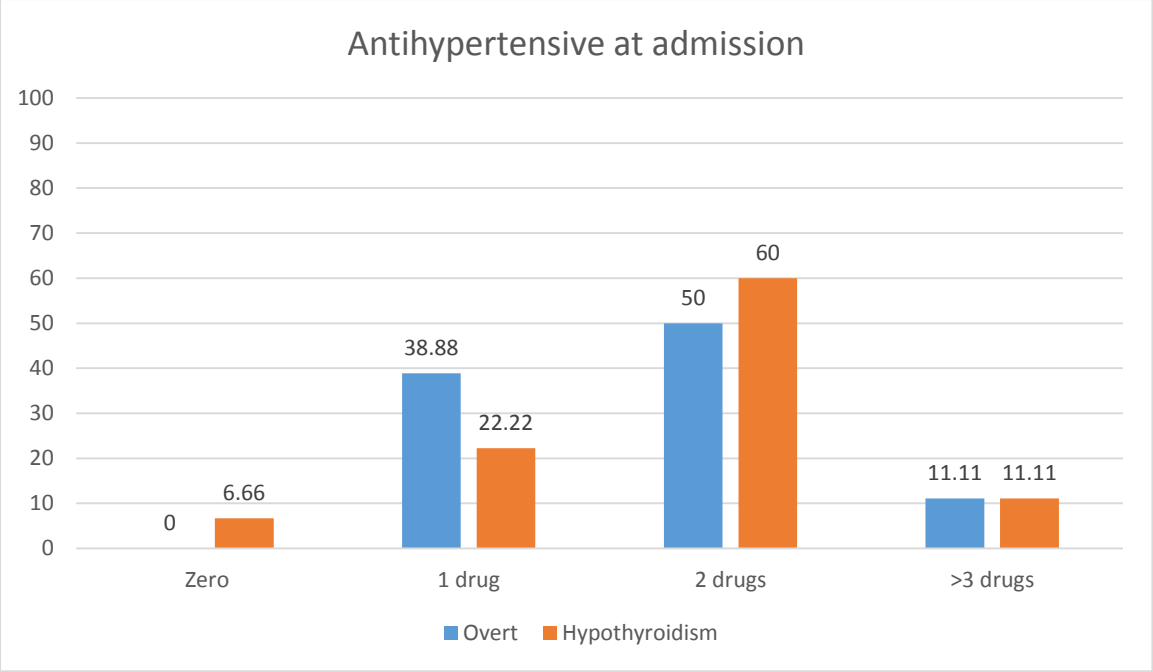


Antihypertensive medications:

When compared the need of antihypertensive medications among the two groups:

1. At presentation:

It was noted that there was small number of women who did not require antihypertensive in subclinical hypothyroidism group though it was statically not significant. Though other findings was not significant.



2. At Discharge:

The number of women requiring antihypertensives at discharge was similar in both the arms and when compared the number of drugs most of the women in both the group required only one single antihypertensive medication for blood pressure control. There was only one women in overt hypothyroidism group requiring 3 antihypertensive medications and only 2 women in subclinical group who required 2 antihypertensives at discharge.

3. Post natal period:

During the follow up visit, the need of antihypertensive medications was noted to be similar in either of the groups expect that one woman in overt hypothyroidism group continued to required 3 antihypertensives even after 3 months post natal for blood pressure control.

2. **Comparison between the women with subclinical hypothyroidism with thyroid antibodies positive and with antibodies negative:**

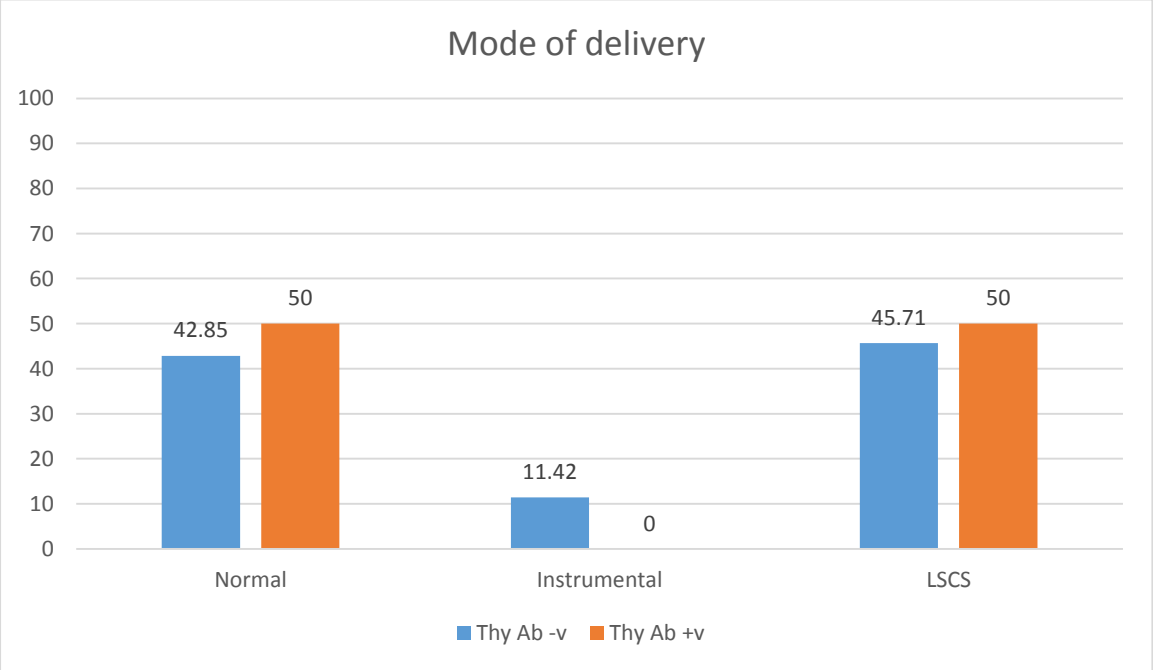
Among the women with subclinical hypothyroidism , there was 22 percent(10 women) of women who were found to be thyroid antibodies positive.

When compared the different outcomes among the women with thyroid antibodies positive with subclinical hypothyroidism , this was observed:

The clinical presentation was similar in both to groups.

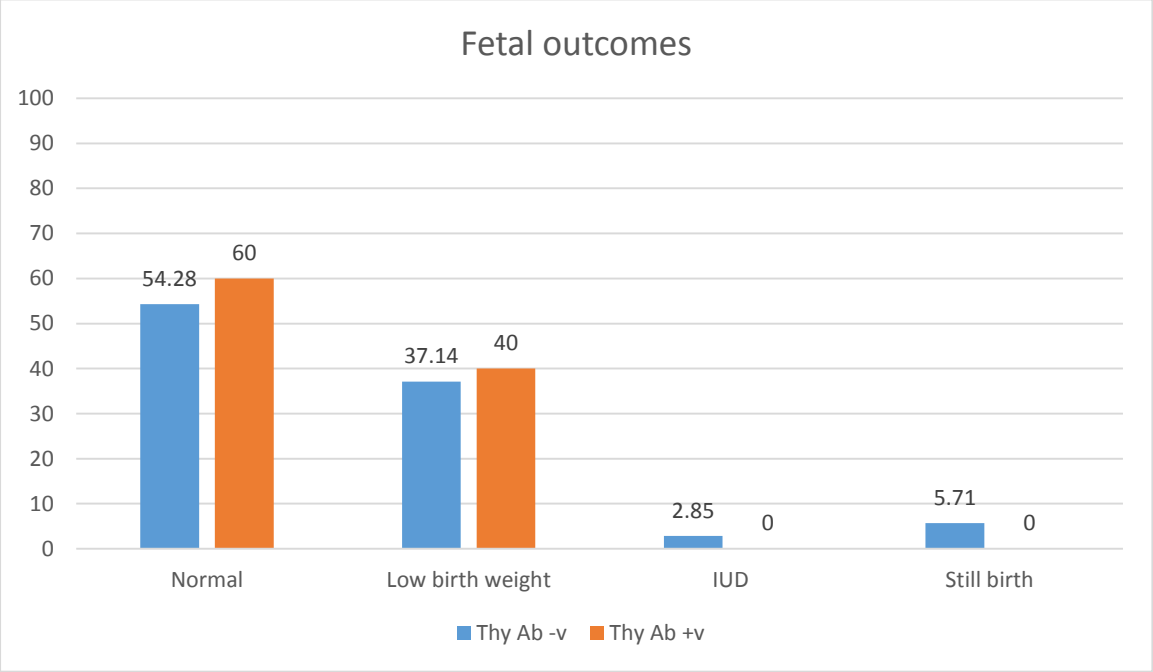
Maternal outcomes:

The maternal outcomes in terms of mode of delivery, it was noted there was no statistical difference between the two groups though instrumental deliveries were seen more among women with thyroid antibodies negative .



Fetal outcomes:

When Fetal outcomes were compared, it was noticed that intrauterine death and still birth were more among women with thyroid antibodies being negative as compared to women with subclinical hypothyroidism with thyroid antibodies being positive. There was no difference found with regards to the gestational age at the delivery. This difference can be due to the very small number of the women in each arm and hence it is not statistically significant.

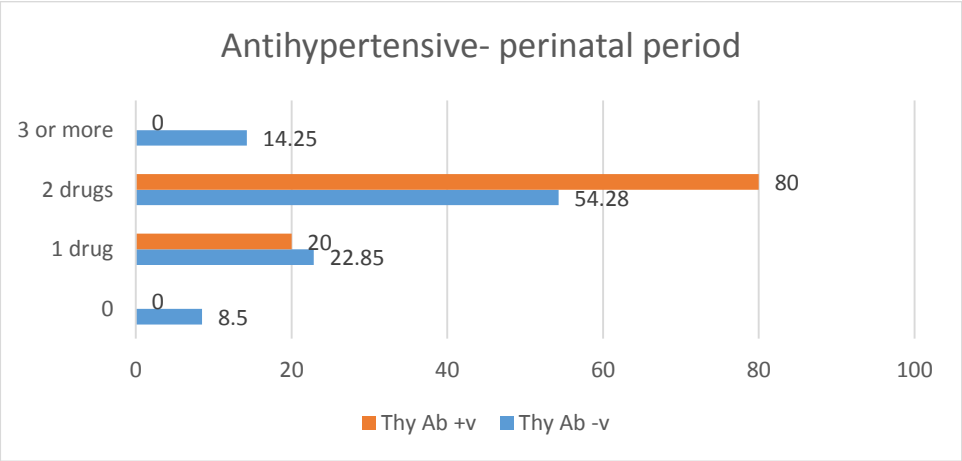


Antihypertensive medications:

1. Perinatal period:

When compared the numbers of antihypertensive required majority of the women required 2 antihypertensive in thyroid antibody positive group, though none required more than 2 antihypertensives . But it was noted that around 14.25 percent women

required 3 or more than 3 drugs of blood pressure control during perinatal period in thyroid antibody negative arm and there were around 8.5 percent women among thyroid antibody negative who did not require any antihypertensive for blood pressure control.



2. At discharge:

In both group 50 percent required antihypertensive medications at discharge. Among the women with thyroid antibodies positive , it was noted that all the women required only 1 antihypertensive , there was none who required more than one, whereas among the women with thyroid antibodies negative, there was 5.7 percent women requiring 2 antihypertensives and 45.71 percent required only 1 antihypertensive at discharge.

3. Post natal period:

There was none who required antihypertensive for more than 2 visits and none went on to chronic hypertension. The requirement of the antihypertensives was noted to be similar in both the arm.

DISCUSSION

PRIMARY OBJECTIVE:

1. **To measure the prevalence of hypothyroidism**

A study published in 2017 by Dima et al , showed prevalence of hypothyroidism was found to be 17.1% in first trimester, 14% in second trimester and 5% in third trimester among pregnant women in Lebanon. [lviii]

In 2017 a study published by Divya et al among pregnant women in their first trimester in Trivandrum, showed the prevalence of hypothyroidism being 5.6 percent had subclinical hypothyroidism.[lix]

Other study done in 2015 in South India a tertiary care centre by Nabhi et al, the prevalence of hypothyroidism was found to be 19.41 percent. [lx]

According to the 'THYDOR' Thyroid disorder in Pregnancy study , we found that the prevalence of hypothyroidism was found to be about 29.3 percent in women presenting with pre-eclampsia to the department of obstetrics and gynaecology.

This study showed increased prevalence of the hypothyroidism (subclinical and overt) among pregnant women which can be secondary to probably autoimmune thyroiditis.

SECONDARY OBJECTIVES :

- **To study the contribution of thyroid disorder to the maternal outcomes ::**

The studies done previously showed that in hypothyroidism complicating pregnancy there was increased risk of pre-eclampsia and post partum haemorrhage. [lxi]

A study done by Saki et al in a tertiary care centre in America to assess the adverse complications secondary to the untreated hypothyroidism during and noticed that there was increased risk of preterm deliveries. [lxii] It was also noticed that the route of delivery being caesarean section was higher in women with hypothyroidism around 16.2 percent.[lxiii] Whereas a FASTER Trial done in 15 centres on United stated by Jane et all observed that hypothyroidism or hypothyroxinaemia was not associated with adverse maternal outcomes. [lxiv]

A Indian study done by Sahu et al in 2010 observed that hypothyroidism in women during pregnancy either overt or subclinical is associated with increased pregnancy induced hypertension, intrauterine growth restriction and demise and increased caesarean section in mother. [lxv] Whereas study done by the Vimal et al showed that hypothyroidism was associated with increased risk of miscarriages.[lxvi]

According to the "THDOR" study , there was no difference found between the two group with regards to the maternal outcomes in terms of mode of delivery, complications of pre-eclampsia. The route of delivery and gestation age at delivery was found to be similar in either groups. The noted complications with regards to pre-eclampsia was also same in percent with no statistical difference being found in both the groups.

- **To assess the time to normalisation of blood pressures pre and post delivery ::**

The time to normalisation of the blood pressure was found to be similar in both group. There was no previous study done to assess the time to normalisation of blood pressure in women with hypothyroidism.

- **To assess the number of medications required for the normalisation of blood pressure::**

With regards to number of medication required though women with hypothyroidism had increased number of the number of antihypertensive required but it was statically significant . It was noted that during the perinatal period the number of antihypertensive medications required was higher in women with hypothyroidism though it was statically significant, whereas the need of antihypertensive medications required in the immediate postpartum period and during follow up visits were found to be similar in both the group.

- **To study the fetal outcomes::**

There was study done by Saki et all in America, showed that neonates born to mothers with hypothyroidism had increased preterm deliveries and IUGR rates as compared to neonates born to mother with normal functioning thyroid. It was found to be 2.18 times increased risk of

intrauterine growth retardation in neonates to mother with hypothyroidism as compared to normal functioning thyroid. [lxvii]

A study done by Ezzedine et all to look for the correlation between hypothyroidism and pregnancy outcomes , showed increased miscarriages to about 2.9 times along with increased pre term delivery with prevalence being 14.6%.There was also increased instrumental and caesarean section noted among the group with hypothyroidism. [lxviii]

A study by Lazarus et al in United kingdom, showed prevalence of 2.5 percent during pregnancy with impaired intelligent quotient noted among children born to women with hypothyroidism**.** [lxix]

In a study done by Ajmani et al, there was adverse fetal outcomes noted in group with hypothyroidism which included spontaneous abortion 16.6%, preterm birth 33.3%, low birth weight 50% , intrauterine growth retardation 25% and fetal death 16.6% as compared to the euthyroid patients.[lxx]

There have been various studies which showed increased prevalence of hypothyroidism in pregnant women in North India. The studies have shown increased maternal and fetal complications secondary to hypothyroidism during pregnancy.[lxxi]

Ajmani et al studied in a tertiary care centre in Delhi, the adverse effects of hypothyroidism in mother and its effects on fetal outcome and found that the adverse fetal outcomes such as spontaneous abortion, preterm deliveries and intrauterine growth retardation was higher in new born born to mother with hypothyroidism during pregnancy as compared with new born born to mother with normal thyroid function. [lxxii]

Though THYDOR study did not show any difference in terms of fetal outcomes (birth weight, intrauterine deaths and still birth and maturity) in either of the group, hence hypo functioning of the thyroid in mother, has not shown any significant association in terms of fetal adverse outcomes.

Subgroup analysis:

1. **Subclinical and overt hypothyroidism:**

Abalovich et al did a study to assess the adverse outcomes secondary to the hypothyroidism among pregnant women, and they noticed that the fetal outcomes in terms of abortion and preterm delivery was higher in women with subclinical hypothyroidism as compared to overt hypothyroidism, which can be secondary to the initiation of the treatment in women with overt hypothyroidism.[lxxiii]

A study done in Bangladesh by Sharmeen et al noticed that the pregnancy induced hypertension, intrauterine death and neonatal complications such as respiratory distress were more among the women with overt hypothyroidism when compared with with subclinical hypothyroidism.

When compared the women with subclinical and overt hypothyroidism , it was noted that intrauterine death was found to be higher in women with overt hypothyroidism as compared to women with subclinical hypothyroidism. There was no other significant

difference found among the women with regards to the maternal outcomes and antihypertensive requirement.

2. **Thyroid antibody positive and its correlation to maternal and fetal outcomes:**

A Meta-analysis done by Sima et al demonstrated that thyroid antibodies positivity among women with hypothyroidism was found to be 20 percent and it was not associated with feto-maternal complications. There was no difference found among women with thyroid antibodies positive and negative with regards to the fetal and maternal outcomes and hence its role was found to be controversial.[lxxiv]

Our study also found the prevalence of women with subclinical hypothyroidism with thyroid antibodies positive being around 22 percent. There was no statically significant difference found with regards to the maternal outcomes though it was noted that the intrauterine death and still birth were more in women with thyroid antibodies negative. When antihypertensives requirement and other outcomes were compared there was no significant difference found, similar findings as in the previous studies done.

CONCLUSION & LIMITATIONS

CONCLUSION:

The prevalence of the hypothyroidism was found to be higher in the women with pre-eclampsia. Screening for the thyroid disorders in the women might help in reduction in the complications and improve maternal and fetal outcomes, though this study did not show any significant difference in outcomes among the groups.

It was noted that the women with hypothyroidism required more antihypertensive medications during the perinatal period as compared to the women with normal thyroid function, hence hypothyroidism in women during pregnancy has association with worsening blood pressure and increase number of antihypertensive requirement. With regards to the thyroid antibodies correlation with maternal and fetal outcomes failed to establish significant correlation between thyroid antibody positivity and maternal and fetal adverse outcomes.

There have been studies done showing maternal hypothyroidism leading the adverse fetal outcome mainly noticed during their early childhood and affecting the intelligence quotient, though this study have not looked for the same , further studies can be done to assess the maternal and fetal outcomes over a long duration.

LIMITATIONS

The limitations of the studies were as follow:

1 .It was done as a univariate analysis hence many women were excluded

2. Most of the women presenting with pre-eclampsia have multiple risk factors precipitating the outcomes both maternal and fetal. Hence only thyroid disorders as an individual risk factor , is a drawback though further studies are required to study thyroid disorder with other risk factors during pregnancy and its outcome.

3. Most of the women had only one follow up visit which can be contributed to the fact that the waiting time in outpatient department with a new born was long and hence women did not come for proper follow up visits.

4. The numbers were small to study the effects of thyroid disorder and effects of subclinical and overt hypothyroidism in pregnancy and also correlation between thyroid antibody positivity and its adverse outcomes.

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ANNEXURES

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

August 22, 2016

Dr. Prashansa Sadanshiv,
Post Graduate Registrar,
Department of Medicine - 3,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Hypothyroidism in pre-eclampsia (THYDOR study)
Dr. Prashansa Sadanshiv (Employment Number:29488), Registrar General medicine unit 3, Dr. Sowmya Sathyendra, Medicine, Dr.Nihal Thomas, 20917, Endocrinology, Dr. Anuja Abraham, 31916, OG, Dr. Santosh Benjamin, 31318, Dr. Reeta vijaya Selvi, 50600, OG , Mr. Bondo DianJoseph, 31696, Clinical biochemistry, Dr. Sudha Jasmine, ? 8296, Medicine Unit III, Dr.Riddhi Das gupta, 20917, Endocrinology, Dr.Vishalakshi, Biostatistics

Ref: IRB Min No: 10047 [OBSERVE] dated 04.04.2016

Dear Dr. Prashansa Sadanshiv,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY (ETHICS COMMITTEE)
Institutional Review Board
Christian Medical College, Vellore - 632 002.

Cc: Dr. Sowmya Sathyendra, Department of Medicine - 3, CMC, Vellore. 1 of 4

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Ref: IRB Min No: 10047 [OBSERVE] dated 04.04.2016

Dear Dr. Prashansa Sadanshiv,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Hypothyroidism in pre-eclampsia (THYDOR study)" on April 04 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Patient Information Sheet and Informed Consent Form (English, Tamil, Hindi,Telugu)
3. Clinical Research Form
4. Cvs of Drs. Anuja Abraham, Vishalakshi, Santosh Benjamin, Nihal Thomas , Reeta vijaya Selvi, Riddhi Das gupta, Sudha Jasmine, , Sowmya Sathyendra, Mr. Bondo DianJoseph
5. , No. Of documents 1 - 3

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on April 04th 2016 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore - 632002.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist &Epidemiologist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Visalakshi, J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil,BL	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. B. J. Prashantham	MA(Counseling Psyc MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB, Director, Chri Counseling Centre, Vellore	External, Social Scientist
Dr. Rajesh Kannangai	MD, PhD	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MD, DNB(Endo), Phd(Endo)	Professor, Endocrinology, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse

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Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Sathish	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Irian Suvarnsam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Rema Prabhu	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of with drawals for the study entitled: "Hypothyroidism in pre-eclampsia (THYDOR study)" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 50,000/- INR (Rupees Fifty Thousand) will be granted for 1 year and out of which a maximum of Rs 5000/- can be spent for stationary, printing, Xerox etc and computer charges if computers used are within the institution)

Yours sincerely

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS, MD, DM
SECRETARY - IEC
Institutional Review Board
Christian Medical College, Vellore

CHRISTIAN MEDICAL COLLEGE , VELLORE

DEPARTMENT OF GENERAL MEDICINE

INFORMATION

THYROID DISORDER IN PRE-ECLAMPSIA(THYDOR STUDY)

Introduction:

You are invited to participate in a study to assess the incidence of thyroid disorder in pre-eclampsia and its maternal and fetal outcome. During the admission in hospital with pre-eclampsia thyroid stimulating hormone test along with thyroid function test and if found to have hypothyroid they will be tested for thyroid antibodies and treatment will be initiated for the same. You will be followed by till 12 weeks after delivery till the blood pressure is normalized. The identity of all subjects agreeing to participate in this study will remain concealed and no information that would result in your identification will be collected.

Your participation is voluntary:

Your participation in this study is voluntary. This form provides you with information regarding the purpose of this study, how it will be conducted and how it affects you.

If you decide to participate in this study you will be asked to sign the consent form provided to you. You are free to withdraw from the study at any time after signing the form without prior explanation, if you wish to do so.

You are free to decline from participating in this study if you do not wish to do so and do not need to give an explanation for the same. Declining participation in this study will not effect your medical care.

Kindly take the time to read this form carefully. You are free to consult with the family, friends or your treating physician prior to making your decision regarding participation in this study.

Background:

Thyroid disorder is common in women and found to be common in pregnancy and goes undetected. It has effect both on mother and the growing baby. It can cause hypertension, pre-eclampsia in mother and at the same time can effect the growth of the baby. It can lead to chronic hypertension in mother and mental retardation the baby born to the mother. This study is to see the incidence of thyroid disorder in women with pre-eclampsia , the maternal outcome and if thyroid disorder is associated with chronic hypertension.

What is the purpose of the study?

The purpose of the study is to find the incidence of thyroid disorder in women with pre-eclampsia and its associated complications and maternal and fetal outcome and check for the correlation between thyroid disorder and chronic hypertension.

Who can participate in the study?

All pregnant women coming to obstetric department for the first time to labour room and ward with pre-eclampsia from the month of May 2016 to December 2016 will be eligible to participate in this study. The study aim is to find the incidence of thyroid disorder in women with pre-eclampsia and its maternal and fetal outcome with long term effect of hypothyroidism on women. The patient would require to give written consent for the participation in the same. In case the patient is unable to give an informed consent her relative should be wiling for the same.

Who should not participate in the study?

If you / your relative are unable or unwilling to give consent for the participation in this study you would not be included in the same.

If you have thyroid disorder previously and is on thyroid supplement then you would not be included in the same.

If you have history of hypertension during previous pregnancy, diabetes during previous pregnancy or in present pregnancy then you would not be included in the same.

What does the study involve?

This study will take place in Obstetric department in labour room and ward. Women with pre-eclampsia presenting for the first time with no prior history of thyroid disorder and in absence of risk factors known to attribute to gestational hypertension and pre-eclampsia will be advised for blood test for thyroid stimulating hormone levels and

thyroid function test. Women will be followed up to 12 weeks after delivery to assess for the normalization of the blood pressure.

What do you have to do ?

At the time of presentation to labour room and ward with pre-eclampsia, you be will asked for the blood test for the thyroid stimulating hormone and thyroid function test. In case if you are found to have hypothyroidism you will be tested for thyroid autoantibodies for further treatment.

What are the possible harms of taking part in the study?

This study require blood sampling once . Following the blood sampling you can feel light headed and can have injection site burning and pain. In most cases the likely of these complications are less though can happen and need to be watched for.

What are the benefits of participating in this study?

This study may or may not benefit you directly. The investigators hope that information gained from this study will be use for the pregnant women in future for the screening of thyroid disorder and monitoring for the complications.

Will taking part in this study affect your treatment in any way?

All the subjects will receive the same medical treatment as they would receive normally if they were not participating in the study.

What happens if you decide to withdraw from participating in this study?

Your participation in this study is entirely voluntary and you are free to withdraw permission to participate in this study. Doing so will not affect your treatment in this hospital in any way. The study doctor may decide to discontinue the study at any time or exclude you from the study at anytime if she/he feels that it in your best interest. If you choose to enter the study and then withdraw at a later date, the data obtained from you may be used for analysis purpose.

What happens if something goes wrong?

Your rights as a patient remain the same irrespective of the participation in this study and will not be affected by signing this consent form.

Remuneration/compensation:

Participants will not be paid for taking part in this study

Will your personal details be kept confidential?

The results of this study may be published in a medical journal, however your confidentiality will be respected and no information regarding your identity will be released without your consent. Your medical records may be reviewed by persons associated with study without your additional consent should you agree to take part in the study.

Who do you contact if you have any questions or concerns during the study?

If you have any further questions please contact Dr.Prashansa Sadanshiv via email Medicine3@cmcvellore.ac.in

CLINICAL RESEARCH FORM

HYPOTHYROIDISM IN PRE-ECLAMPSIA (THYDOR STUDY)

DEMOGRAPHIC DATA

- Serial no:
- Date of entry:
- Age :
- Hospital number :
- Phone number :

HISTORY

- Gravida , para , living , abortion :
- Gestational age at presentation :
- Expected date of delivery :
- Education :
- Occupation :
- Income annual :
- Geographic details :
- Previous Obstetric history :
- Outcome of previous pregnancies :

Pregnancy number	Maternal complications	Outcome	Gest age at delivery	Mode of delivery	Foetal/neonatal complications
1					
2					
3					

Prior Medical history(diabetes/hypertension/thyroid disorder are excluded:

- Other medical history :
- Medication history:

Personal:

- Smoking :
- Alcohol :

Family history :

EXAMINATION

- Pre-pregnancy weight/First trimester pregnancy weight :
- BMI :
- Height :

- Present Weight :
- Blood pressure :
- Respiratory system :
- CNS system:
- Cardiac system:

INVESTIGATIONS

- GTT :
- Proteinuria:
- Creatinine:
- Platelets:
- SGOT:
- SGPT:
- TSH:
- T3:
- T4:
- Ftc :
- TPO:

- Outcome of this pregnancy with complications :

Maternal:

Fetal:

ANC/PNC visits/Blood pressure/ medications:

Date	Gestational age/PND	Blood pressure	Medications

CONSENT FORM::

Study Title: *hypothyroidism in pre-eclampsia*

Study number:

Participant's name:

Date of birth/ age in years:

I_____

_____, son/daughter/wife

of_____

Declare that I have read the information sheet provided to me regarding this study and have clarified any doubts that I had.

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment of legal rights

I also understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access.

I understand that my identity will not be revealed in any information released to third parties or published.

I voluntarily agree to take part in this study.

Name:

Signature:

Date:

Name of witness:

Relation to participant:

Date:

THESIS DATA

idno	doa	age	edu	occup	gestage	dod	para	live	
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215 #########	33	3	1	31.3 #########	0	0

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fthy	preweig	wgt	ht	bmi	sbp	dbp	papile	creps	
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	2	48	62	147	22	160	100	2	2
	2	60	72	164	23	140	106	2	2
	2	58	64	154	24	200	108	2	2
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	2	62.6	71	163	23.56	140	100	2	2
	2	54	66	154	22.7	160	100	2	2
	2	56	80	161	21.6	160	100	2	2
	2	58	66	168	20.5	200	100	2	2
	2	56	78	160	21.8	140	100	2	2
	2	60	73	153	25	150	100	2	2
	2	52	68	156	21.3	140	100	2	2
	2	53	62	150	23.56	150	100	2	2
	2	68	76	167	24.3	140	100	2	2
	2	55	70	160	21.4	200	100	2	2
	2	35	50	145	16.6	140	106	2	2
	2	44.5	46.5	165	16.3	160	100	2	2
	2	64	76	157	25	150	106	2	2
	2	48	58	156	19.72	140	103	2	2
	2	48	68	157	19.4	140	108	2	2
	2	67	77.2	186	19.16	130	100	2	2
	2	54	70	160	21.09	150	100	2	2
	2	52	77	150	23.1	150	100	2	2
	2	38	48	146	17.8	156	100	2	2
	2	60	90	156	24.6	150	106	2	2
	2	65	83	162	24.7	150	100	2	2
	2	56.4	68	157	22.8	150	102	2	2
	2	60.9	72	160	23.79	140	100	2	2
	2	50	59	156	22.2	140	100	2	2
	2	42	53	146	19.7	190	120	2	2
	2	56	72	160	21.8	170	120	2	2
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2	44	50	148	20.9	170	108	2	2
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2	60	73	165	22.04	150	100	2	2
2	48	62	152	20	166	108	2	2
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2	62	80	159	24.5	140	100	2	2
2	46.01	58	152	19.95	150	100	2	2
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2	40	47.7	151	17.54	150	104	2	2
2	60	70	162	22.86	140	110	2	2
1	56	72	164	20.82	200	100	2	2
2	50	62	152	21.64	160	110	2	2

2	52	68	154	21.93	150	100	2	2
2	54	67	150	24	140	102	2	2
2	60	72	158	24.08	200	120	2	2
2	51.8	60	158	20.75	146	100	2	2
2	56	72	162	21.34	140	108	2	2
2	50	62	156	20.55	150	100	2	2
2	57	70	158	22.83	150	100	2	2
2	66	76.6	163	24.4	150	102	2	2
2	50	60	161	19.29	190	100	2	2
2	55	62	151	24.12	140	100	2	2
2	39	48.96	145	18.55	150	110	2	2
2	50	58	156	20.55	180	106	2	2
2	51	64	157	20.69	160	110	2	2
2	50	57.6	157	20.28	160	100	2	2
2	65	80	168	23.03	170	106	2	2
2	52	77	153	22	140	100	2	2
2	65	78	160	25	148	102	2	2
2	54	62	160	21.09	140	108	2	2
2	45	54	156	18.49	140	100	2	2
2	55	62	160	21.48	150	110	2	2
2	50	62.68	154	21.08	140	108	2	2
2	50	69.4	154	21.08	170	100	2	2
2	42	63	153	17.94	150	100	2	2
2	45	60	156	18.49	240	100	2	2
2	57	68	168	20.2	180	100	2	2
2	45	56	160	17.58	140	106	2	2
2	58	70	164	21.56	130	102	2	2
2	50	67	162	19.05	140	102	2	2

s3	edema	ff	seizure	gtt	pronur	creat	plt	sgot
	2	2	2	2	1	2	0.38	441000	20
	2	2	2	2	1	4	0.45	198000	14
	2	2	2	2	1	1	0.51	300000	20
	2	2	2	2	1	2	0.8	99000	53
	2	2	2	2	1	1	0.32	216000	17
	2	2	2	2	1	1	0.55	229000	21
	2	2	2	2	1	1	0.46	327000	18
	2	2	2	2	1	2	0.45	241000	22
	2	2	2	2	1	1	0.39	188000	27
	2	2	2	2	1	2	0.52	326000	24
	2	2	2	2	1	1	0.42	219000	19
	2	2	2	2	1	1	0.5	320000	19
	2	2	2	2	1	1	0.63	287000	19
	2	2	2	2	1	1	0.49	267000	15
	2	2	2	2	1	2	1.1	67000	33
	2	2	2	2	1	1	0.46	149000	23
	2	2	2	2	1	1	0.4	269000	15
	2	2	2	2	1	1	0.42	186000	14
	2	2	2	2	1	1	0.48	236000	16
	2	2	2	2	1	1	0.56	202000	14
	2	2	2	2	1	1	0.48	306000	23
	2	2	2	2	1	2	0.63	220000	13
	2	2	2	2	1	1	0.5	399000	15
	2	2	2	2	1	1	0.39	197000	16
	2	2	1	2	1	2	0.59	331000	15
	2	2	2	2	1	2	0.6	165000	16
	2	2	2	2	1	1	0.4	167000	14
	2	2	2	2	1	1	0.6	148000	17
	2	2	2	2	1	1	0.43	197000	14
	2	1	2	2	1	2	0.85	164000	22
	2	2	2	1	1	2	1.13	205000	134
	2	2	2	1	1	1	0.49	254000	18
	2	2	2	2	1	1	0.5	16600	11
	2	2	2	2	1	1	0.49	268000	14
	2	2	2	2	1	2	0.6	208000	14
	2	2	2	2	1	1	0.57	330000	17
	2	2	2	2	1	1	0.6	183000	31
	2	2	2	2	1	2	0.68	196000	19
	2	2	2	2	1	2	0.57	166000	11
	2	2	2	2	1	2	0.6	232000	29
	2	2	2	2	1	2	0.7	180000	27
	2	2	2	2	1	1	0.36	165000	20
	2	2	2	2	1	1	0.58	231000	26
	2	2	2	2	1	1	0.5	236000	12
	2	2	2	2	1	2	0.66	342000	12
	2	2	2	2	1	1	0.6	185000	22

2	2	2	2	1	2	0.47	236000	21
2	2	2	2	1	2	0.43	198000	18
2	2	2	2	1	2	0.54	200000	10
2	1	2	2	1	3	0.7	240000	16
2	2	2	2	1	2	0.64	294000	15
2	2	2	2	1	1	0.6	158000	15
2	2	2	2	1	1	0.4	213000	19
2	2	2	2	1	1	0.9	298000	24
2	2	2	2	1	2	0.7	222000	20
2	2	2	2	1	1	0.65	187000	15
2	2	2	2	1	2	0.6	159000	21
2	2	2	2	1	2	0.6	342000	12
2	2	2	2	1	3	0.73	236000	23
2	2	2	2	1	2	0.42	19	10
2	2	2	2	1	2	0.64	269000	12
2	2	2	2	1	2	0.63	175000	17
2	2	2	2	1	2	0.49	160000	21
2	2	2	2	1	1	0.52	178000	18
2	2	2	2	1	2	0.51	117000	19
2	1	2	2	1	3	0.6	220000	14
2	2	2	2	1	2	0.52	223000	14
2	1	2	2	1	2	0.59	175000	26
2	2	2	2	1	2	0.49	225000	22
2	1	2	2	1	2	0.5	148000	17
2	1	2	2	1	1	0.5	71000	37
2	2	2	2	1	2	0.3	336000	14
2	2	2	2	1	2	0.5	235000	16
2	2	2	2	1	2	0.7	334000	19
2	1	2	2	1	3	0.86	86000	69
2	1	2	2	1	2	0.32	232000	46
2	2	2	2	1	1	0.75	218000	15
2	1	2	2	1	2	0.63	231000	19
2	1	1	2	1	2	0.82	120000	28
2	2	2	2	1	1	0.55	271000	23
2	1	1	2	1	2	0.56	284000	12
2	1	1	2	1	3	0.9	142000	184
2	2	1	2	1	1	0.53	153000	36
2	1	2	2	1	1	0.38	246000	10
2	2	2	2	1	1	0.54	230000	14
2	2	2	2	1	1	0.7	260000	32
2	2	2	2	1	1	0.48	306000	23
2	2	2	2	1	1	0.5	354000	40
2	2	2	2	1	1	0.47	201000	14
2	1	1	2	1	3	1.33	68000	37
2	2	2	2	1	1	0.7	280000	19
2	2	2	2	1	1	0.46	281000	24
2	2	2	2	1	1	0.4	250000	14

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2	2	2	2	1	1	0.44	199000	17
2	2	2	2	1	2	0.3	242000	10
2	2	2	2	1	1	0.49	290000	19
2	1	2	2	1	1	0.58	284000	12
2	2	2	2	1	1	0.82	120000	21
2	2	2	2	1	2	0.5	247000	12
2	2	2	2	1	1	0.46	269000	26
2	1	2	2	1	1	0.53	250000	30
2	2	1	2	1	1	0.89	254000	23
2	1	2	2	1	2	0.44	199000	17
2	2	2	2	1	1	0.6	243000	10
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2	2	2	2	1	1	0.3	286000	19
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2	1	2	2	1	2	0.64	286000	18
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2	1	2	2	1	2	0.45	212000	27
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2	2	2	2	1	1	0.5	212000	21
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2	2	2	2	1	1	0.5	194000	15
2	2	2	2	1	1	0.57	185000	26
2	2	1	2	1	2	0.4	210000	15
2	1	2	2	1	2	0.7	144000	22
2	2	1	2	1	2	0.5	148000	10
2	1	2	2	1	2	0.8	253000	31
2	1	1	2	1	2	0.6	226000	23
2	2	2	2	1	2	0.54	146000	20
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2	2	2	2	1	1	0.6	176000	33
2	2	2	2	1	1	0.3	172000	25

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2	1	1	2	1	2	0.42	267000	14
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2	1	2	2	1	1	0.3	127000	25
2	2	1	2	1	1	0.48	158000	15
2	1	2	2	1	2	0.36	228000	14
2	2	2	2	1	2	0.56	205000	17
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2	2	2	2	1	1	0.4	157000	16
2	1	1	2	1	3	0.5	190000	16
2	2	2	2	1	1	0.4	410000	15
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2	1	1	2	1	2	0.8	302000	15
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2	1	2	2	1	3	0.7	252000	15
2	2	2	2	1	1	0.48	158000	15
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2	2	2	2	1	1	0.79	319000	30
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2	1	1	2	1	2	0.54	246000	14
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2	2	2	2	1	1	0.64	173000	17
2	1	1	2	1	2	0.72	271000	14
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2	1	2	2	1	1	0.63	90000	17
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2	1	1	2	1	3	0.53	189000	26
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2	2	2	2	1	3	0.6	199900	25
2	2	2	2	1	1	0.46	286000	18
2	2	2	2	1	1	0.8	261000	102
2	2	2	2	1	1	0.6	184000	45
2	2	2	2	1	1	0.43	384000	125
2	2	2	2	1	2	0.54	200000	18
2	2	2	2	1	1	1.8	216000	25
2	2	2	2	1	1	0.4	185000	14
2	2	2	2	1	1	0.6	250000	26
2	2	2	2	1	1	0.54	203000	14
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2	1	2	2	1	1	1.7	250000	16
2	2	2	2	1	1	0.86	480000	17
2	1	1	2	1	1	0.85	136000	197
2	2	2	2	1	1	0.74	174000	49

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2	2	2	2	1	1	0.6	300000	17
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2	2	2	2	1	1	0.6	160000	17
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2	2	2	2	1	1	0.4	165000	16
2	1	2	2	1	3	0.478	265000	24
2	2	2	2	1	2	0.5	425000	21
2	1	2	2	1	4	0.41	296000	17
2	1	1	2	1	4	0.63	387000	19
2	1	2	2	1	2	0.42	156000	15
2	1	1	2	1	1	0.5	236000	23
2	2	2	2	1	1	0.71	174000	29
2	2	2	2	1	2	0.54	348000	11
2	2	2	2	1	2	0.4	157000	13
2	1	2	2	1	1	0.73	147700	24
2	2	2	2	1	1	0.52	219000	22
2	2	2	2	1	2	0.76	264000	25
2	2	2	2	1	1	0.52	260000	17
2	1	1	2	1	1	0.74	245000	15
2	1	2	2	1	1	0.84	324000	17
2	1	1	2	1	3	0.47	150000	14
2	1	2	2	1	2	0.59	180000	24
2	2	2	2	1	2	0.52	180000	16
2	2	2	2	1	1	0.6	282000	58
2	2	2	2	1	2	0.4	337000	18

sgpt	tsh	t4	t3	ftc	thyab	anit	fetoutcom	mod	
	13	1.7					1	2	3
	8	5.1	4.9	90	3	28	2	1	1
	14	3.7	2.9	70	0.4	35.8	1	1	3
	40	6.4	3.02	66	0.6	1300	2	3	1
	7	4.5	4.5	80	1	28	1	1	3
	15	1.4					0	1	1
	20	1.6					1	1	1
	20	2.8	4.8	154	1.1	28	2	2	1
	21	1.3					2	2	3
	10	7.7	4.9	163	0.95	28	1	1	3
	17	1.75					1	1	2
	10	1.6					1	1	2
	26	2.4					1	1	1
	10	1.4					1	2	3
	126	0.46					2	1	3
	9	6.4	3.8	69.36	0.7	39.8	1	1	2
	6	1.6					1	3	1
	9	1.4					1	1	3
	7	9.2	4.8	86.57	1.35	28	1	1	3
	10	4.6	4.9	132	0.98	28	2	2	3
	12	0.7					1	1	3
	6	4.6	4.8	85	0.86	29.7	2	1	1
	8	4.4	3.8	77.58	0.69	1300	2	1	2
	7	1					1	2	3
	14	2.5	5.1	74.6	0.69	28	1	2	3
	7	1.4					2	1	3
	5	1.3					1	1	1
	6	0.9					1	1	1
	10	2.1					1	1	1
	8	3.3	7.2	92	1.1	28	3	1	2
	26	1.2					3	3	1
	11	3.8	3.9	70	0.59	1011	2	3	3
	7	2.3					2	1	1
	8	2.1					2	1	2
	6	2.54					1	1	2
	16	1.5					1	1	2
	12	10.8	3.2	69	0.72	1083	2	1	2
	9	1.9					2	1	3
	6	1.1					2	2	3
	40	1.3					3	1	1
	14	0.8					2	1	3
	11	2.4					2	1	1
	19	5.3	6.2	112	0.96	28	2	2	3
	7	2.25					1	1	3
	6	1.9					3	1	1
	12	4.4	4.6	86	0.89	28	2	2	3

15	1.8					2	4	1
12	2.1					3	2	3
6	1.9					2	1	1
10	6.9	2.9	78	0.71	120	3	2	3
17	2.5					3	2	1
9	2.6					1	1	3
9	1.9					3	1	3
13	4.2	5.2	101	0.9		2	2	1
14	4.25	4	88	1.2		2	2	3
5	1.2					1	1	1
12	4.55	4.6	96	1.3		2	2	3
6	1.9					3	2	3
15	1.97					3	2	3
	5.2	5	95	1.4		0	1	1
5	1.6					1	1	1
11	2.34					2	1	1
12	2.1					2	1	1
8	2.5					1	1	1
10	1.2					0	1	3
8	2.1					1	2	3
7	2.3					2	2	3
31	2.1					3	2	3
12	3.7	4.9	95	0.86		2	2	3
10	4.3	6.9	130	1.54		2		
15	1.6					3	1	1
10	2.5					1	1	1
9	2.5					0	1	1
7	8.8	6.4	145	1.3		3	2	1
61	1.6					2	4	1
18	2.3					1	1	1
6	4.2	4.8	88	0.9		2	2	3
15	2					2	2	1
16	1.4					2	1	3
16	1.36					1	2	3
9	2.5					1	2	1
94	0.67					2	2	3
24	1.3					1	1	3
7	2.4					1	1	2
7	2.6	6.7	102	1.01		1	2	3
18	5.7	8	109			1	1	1
12	0.7					1	1	3
26	4.6	9.3	167	0.84		0	1	2
10	2.8					1	1	1
23	3.3	4.67	103	1.3		4	3	1
10	1.2					0	1	1
11	1.19					1	1	1
10	4.1	7.25	164	0.9		1	1	3

13	8.6	3.9	71.08	0.8	263	1	1	1
14	3.4	4.5	810.321	0.79	277	2	1	3
5	0.8					1	2	1
7	2.2					2	1	2
9	2.2					2	2	3
13	0.8					2	2	3
8	1.5					1	2	1
27	8.2	4.1	90	0.701	271.5	1	1	1
15	4.5	5.3	97.4	1.4		2	1	3
31	2.3					2	2	3
10	2.309					2	1	3
7	1.43					1	2	3
12	4.4	4.06	78	0.8	384	1	1	1
7	2.7					1	1	3
10	1.6					1	2	3
14	1					3	2	1
16	2.3					1	1	3
12	0.9					3	2	1
15	1.9					2	2	1
7	1.7					2	2	2
11	1.5					2	3	1
14	1.36					1	2	3
5	1.8					1	1	1
6	1.9					2	1	1
13	2.1					1	2	3
17	1.17					1	1	1
12	5.3	4.6	91	0.94		2	2	1
7	1.566					2	1	1
12	1.9					0	1	1
15	1.8					0	1	3
16	1.5					0	1	3
7	1.2					0	1	3
7	0.67					0	1	1
21	3.1	4.2	80	0.59	43.5	1	1	3
11	2.8	6.2	90	0.94		1	4	1
13	1.6					3	2	1
6	4.3	3.2	73.09	1.001	489	2	1	1
10	1.6					3	1	2
15	9.3	2.1	56	0.4	1118	2	2	1
12	1.2					2	2	3
14	5	2.8	67	0.568	1300	2	1	3
14	2.1					2	2	1
19	5.65	6.35	124.52	1.295		2	2	2
10	2.8					2	4	1
20	1.9					1	1	1
35	5.2	4.2	78.36	1.02	30.3	2	2	1
14	3					3	1	3

9	1.17					2	2	3
7	4.3	3.036	75	0.82	489	2	2	3
254	1.2					2	2	3
17	7.4	6.23	96.56	1.3		2	2	3
7	1.47					2	2	3
7	4.3	2.89	74	0.777	489	3	1	3
10	2.9					1	1	1
8	2.45					1	1	1
11	1.17					2	2	1
10	4.8	7.5	96.58	1.3		0	1	1
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7	1.2					3	2	3
8	2.5					3	4	1
7	3.9	5.26	112	0.95		1	1	1
10	2.32					3	4	1
24	3.27	6.12	98	1.21		3	2	1
7	1.3					2	2	3
5	1.6					2	1	3
29	1.5					3	2	3
14	1.13					1	1	1
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7	3.9	4.7	106	0.88		2	2	3
9	3.5	6.25	163	1.24		2	1	1
9	4.86	5.36	102.35	0.96		3	1	3
9	2.3					2	1	3
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12	5.8	6.89	96.35	0.86		2	1	3
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9	9.3	2.9	66.098	0.05	1118	1	2	1
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8	5.5	7.2	118.64	1.25		2	2	3
4	3.65	6.54	98.36	1.02		2	1	3
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4	2	1	1 labetalol	100	2

PNC DATA SET

idno	pncd	pnc	anthtn	anti1	anti1d	anti1d1	anti2	anti2d
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	2	4		0	0			
	3	0		0	0			
	4	1		labatalol	200			
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	5	3		0				
	6	3		0				
	6	1		0				
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	7	2		0				
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	18	1						
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	19	2		0				
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41	1	7					
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47	2	180	labetalol	100	2		
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50	2	55	enalapril	10	2	metoprolol	50
51	1	30	enalapril	5	2		
52	1	14					
53	1	60					
54	1	21					
55	1	100	labetalol	100	2		
56	1	10					
57	0						
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61	1	15					
62	1	20					
63	1	40					
64	0						
65	1	112					
66	1	80					
67	1	48					
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69	1	15	labetalol	100	1		
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90	2	30	1 amlodipine	10	1	minipress x	5
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